JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.14587 *Journal of Dermatology* 2018; ●●: 1–50

GUIDELINE

Wound, pressure ulcer and burn guidelines – 2: Guidelines for the diagnosis and treatment of pressure ulcers, second edition

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BACKGROUND OF THE DRAFTING OF THE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF PRESSURE ULCERS

Guidelines are documents systematically prepared to support medical experts and patients for making appropriate judgments in particular clinical situations. The Japanese Society of Pressure Ulcers (JSPU) published the Guidelines for the Prevention and Management of Pressure Ulcers in February 2009, which has undergone revisions leading to the publishing of the fourth edition in 2015. Their guideline was not intended solely for physicians, but for nurses, nutritionists, pharmacists, physical therapists, occupational therapists and other health-care professionals; it emphasized the prevention and care over the treatment. On the other hand, the present guideline, "Guidelines for the diagnosis and treatment of pressure ulcers", placed more emphasis on the treatment. Both guidelines shared the same goal: systematically presenting evidence-based recommendations to support clinical decisions in the prevention, care and treatment of pressure ulcers, serving as a tool for improving the quality of diagnosis and treatment of pressure ulcer patients, and improving the care for pressure ulcers in Japan as a whole.

POSITION OF THE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF PRESSURE ULCERS

The Wound, Pressure Ulcer and Burn Guidelines Drafting Committee (Table 1) was composed of members delegated by the Board of Directors of the Japanese Dermatological Association. The committee meetings were held gathering or through email since October 2008, and has drafted the guidelines for wounds in general, and other five related guidelines, including this guideline, by taking into consideration the opinions of the Scientific Committee, the Guideline Committee, and the Board of Directors of the Japanese Dermatological Association. The present guidelines reflect the current standards for diagnosis and treatment of pressure ulcers in Japan. However, the factors that a physician should take into consideration during diagnosis and treatment of a pressure ulcer are more diverse than those of other wounds; the patient's underlying disease, the situation of a care-providing facility, the patient's home and the locoregional conditions in which the patient resides should be considered. It is unlikely that the optimized treatment for an individual patient is in absolute agreement with these guidelines. Any deviation from these guidelines should not be the basis for citation in lawsuits or legal disputes.

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This is the secondary English version of the original Japanese manuscript for Wound, pressure ulcer, and burn guidelines – 2: Guidelines for the diagnosis and treatment of pressure ulcers, second edition published in the *Japanese Journal of Dermatology* 127(9); 1933–1988, 2017.
Received 26 June 2018; accepted 3 July 2018.

Table 1. Wound/Burn Guideline Drafting Committee (the head of each section is underlined)

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MAJOR UPDATED POINTS IN THE SECOND EDITION

- All sections were updated by collecting documents published since the publication of the first edition. A number of new reports were published regarding dressing materials such as polyurethane foam, soft silicone, alginate foam and silver-containing preparations, and each of the new dressing materials was evaluated.
- The depth of a pressure ulcer was described in stages I–IV in accordance with JSPU and National Pressure Ulcer Advisory Panel (NPUAP)/European Pressure Ulcer Advisory Panel (EPUAP)/Pan Pacific Pressure Injury Alliance (PPPIA) pressure ulcer guidelines. In the previous edition, it was described as first–fourth degrees.
- Change in the clinical questions (CQ): The CQ on pain was changed from addressing only the acute phase to all the phases (CQ10). Local control of infection was divided in two, the use of topical agents and that of dressings (CQ20, CQ21).
- These guidelines do not address medical-device related pressure ulcers (MDRPU; i.e. pressure ulcers caused by compression with tubes, foot pumps and so on), which have been an issue in recent years.

SPONSORS AND CONFLICT OF INTERESTS

All expenses required for drafting these guidelines have been borne by the Japanese Dermatological Association, and no aid or financial support has been provided by specific organizations, enterprises or pharmaceutical companies. Furthermore, in the case that a committee member (Table 1) participating in the drafting of these guidelines was involved in the development of a specific, relevant drug, that member abstained from determining to what degree the item in question was recommended. Aside from that, each committee member has no conflict of interest to disclose in the drafting of these guidelines.

COLLECTION OF EVIDENCE

Databases search: The key word search in Medline, PubMed, Japanese Medical Abstracts Society and Cochrane Database of Systematic Reviews, as well as the personal references of the committee members, were performed.

Search period: The studies published between January 1980 and December 2013 were reviewed. More recent publications were also considered, if appropriate.

Adoption criteria: Priority was placed on systematic reviews of randomized controlled trials (RCT) and on individual RCT. If they were not available, cohort studies and case–control studies were adopted. Case series studies were also used as references. Basic research studies were not considered as evidence in recommendation.

CRITERIA FOR THE DETERMINATION OF EVIDENCE AND RECOMMENDATION LEVELS

The criteria adopted in the "Guidelines for the diagnosis and treatment of malignant tumors" described below, published by the Japanese Dermatological Association, were used as a reference for the classification of the evidence levels.

Evidence level classification:

I Systematic reviews or meta-analyses.
II RCT.
III Controlled trials, not randomized, including statistically analyzed comparative studies of pre- and post-treatment.
IVa Analytical epidemiological studies (cohort studies).
IVa Analytical epidemiological studies (case–control studies or cross-sectional studies).
V Descriptive studies (case reports and case series studies).
VI Expert opinions of special committees or individuals.

The *Minds Handbook for Clinical Practice Guideline Development 2014* was referenced for the recommendation levels.

Classification of recommendation levels and descriptions:

Recommendation levels:
1: Recommended.
2: Proposed (as an option).

If the recommendation levels could not be determined, recommendation level "none" may be given.

The recommendations appear with the strength of evidence (defined as A, B, C and D) and the recommendation level as in the following examples:

1. The treatment is recommended for every patient (1A: strong recommendation, based on strong evidence).
2. The treatment is proposed as an option for some patients (2C: weak recommendation, based on weak evidence).
3. It is proposed that treatment not be performed for patients (2D: weak recommendation, based on very weak evidence).
4. It is recommended that treatment not be performed for any patients (1B: strong recommendation, based on moderate evidence).

REVIEW BEFORE PUBLICATION

Before the publication of these guidelines, those of annual progress in drafting were presented in the Annual Meetings of the Japanese Dermatological Association from 2012 to 2015, to solicit opinions from the association members in order to make necessary revisions.

PLANS FOR UPDATES

The present guidelines are scheduled to be updated in the next 3 or 5 years. However, if a partial update becomes necessary, it will be presented on the website of the Japanese Dermatological Association.

DEFINITIONS OF TERMINOLOGY: QUOTED FROM THE TERMINOLOGY LIST OF THE TERMINOLOGY COMMITTEE (CHAIRMAN: DR TAKAO TACHIBANA) OF THE JAPANESE SOCIETY OF PRESSURE ULCERS

Pressure ulcer: External force applied to the body reduces or blocks blood flow in the soft tissue between the bone and the skin surface. If this state continues for a certain period, the tissue sustains irreversible ischemic damage and develops into a pressure ulcer.

Topical agents: Drugs that are applied through the skin or directly to skin lesions for localized treatment. They are prepared by compounding various drugs with a base.

Dressing materials: Modern wound-dressing materials for creating a wet environment for wounds. Conventional sterilized gauze is excluded.

Wound-dressing materials: Wound-dressing materials can be broadly divided into dressing materials (modern dressing materials) and medical materials such as gauze (classic dressing materials). The former are medical materials that provide conditions optimal for wound healing by maintaining a moist environment, and must be used selectively depending on the state of the wound and the amount of exudate. Gauze allows drying of the wound and cannot maintain a moist environment if exudate volume is insufficient. Medical materials other than conventional gauze that provide an optimal environment for wound healing by covering the wound and maintaining moisture may also be called wound-dressing materials or dressing materials.

Occlusive dressing: All dressing methods used to avoid drying of wounds for moist wound healing are called occlusive dressings. This is a collective term for dressings using modern wound-dressing materials other than conventional gauze dressing.

Wet-to-dry dressing: Dressing aimed at debridement performed by applying gauze saturated with physiological saline to the wound, and once the gauze has dried, non-selective removing of foreign material and necrotic tissue adhering to it occurs when it is changed.

Surgical treatments: Surgery, surgical debridement and invasive treatments of subcutaneous pockets.

Physical therapy: Treatment performed by applying stimulation to the body using physical means, which include physical energy such as heat, water, light, ultrashort waves, electricity, ultrasound, vibration, pressure and traction. Thermotherapy, cryotherapy, hydrotherapy, phototherapy, ultrashort wave therapy, electric stimulation therapy, ultrasound therapy, negative-pressure therapy, high-pressure oxygen therapy and traction therapy are variations of physical therapies. These are performed to mitigate pain, promote wound healing and increase the elasticity of tissues such as muscles and ligaments. "Physical therapy" is used as a general term for all these therapies, and the means for the treatment are conventionally called "physical agents" to avoid confusion.

NPUAP pressure ulcer staging system: A classification of depth of pressure ulcers, a staging system proposed by the NPUAP in 1989. Conventionally, pressure ulcers have been classified into stages I, II, III and IV. Recently, however, the category of deep tissue injury (DTI) has been added based on the concept that deep areas may be damaged even without damage to the skin surface. Therefore, according to the new NPUAP pressure ulcer staging system issued in 2007, pressure ulcers are categorized into six stages: (suspected) DTI, stages I, II, III and IV, and unstageable (whether the depth of pressure ulcer is III or IV is impossible to determine).

DESIGN: An assessment scale for evaluating the conditions of pressure ulcers introduced by the Japanese Society of Pressure Ulcers in 2002 as an assessment tool consisting of seven items: depth, exudate, size, inflammation/infection, granulation tissue, necrotic tissue and pocket. There are two types: one used for severity classification representing severe and mild using capital and lowercase letters, respectively, and the other for the evaluation of patient progress by quantifying the healing process to allow monitoring. The latter type exists as the 2002 version, and the 2008 revision (DESIGN-R® with the "R" standing for "rating") was amended to provide a more accurate rating of severity as well as evaluation of the course of pressure ulcers.

Deep tissue injury: The term used by the NPUAP in 2005, meaning a pressure ulcer without epidermal loss (stage I) in which there is a suspicion of damage to tissues deeper than subcutaneous tissue. In the NPUAP pressure ulcer staging system for pressure ulcers revised in 2007, "(suspected) deep tissue injury" was added as a new stage. It may be translated as "deep tissue damage" for damage other than pressure ulcers

Nutrition support team (NST): The Japan Council for Nutritional Therapy (JCNT) calls nutritional management performed appropriately for individual patients and for the treatment of individual disorders "nutrition support" and defines a team of several professions including a physician, nurse, pharmacist, managerial dietician and clinical laboratory technician as the NST.

Erosion: Cutaneous or mucosal loss not extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually heals without leaving a scar.

Ulcer: Cutaneous or mucosal loss extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually leaves a scar after the cure.

Decompression: Reducing contact pressure similarly to that of pressure reduction. Previously, reducing the pressure to less than 32 mmHg, considered to be the internal pressure of capillaries, was defined as decompression, and to 32 mmHg or above as pressure reduction, but this distinction is not made today.

Body pressure-dispersion devices: Devices that reduce the pressure on a unit of body surface area due to contact with a support such as a bed or a chair by widening the contact area or by shifting the area under pressure over time to reduce the pressure at any single site over the long term. Devices used for patients in a recumbent position include special beds, overlay mattresses layered over a bottom mattress, and replacement mattresses to be substituted for conventional mattresses. Devices used for patients in a seated position include cushions placed on chairs and wheelchairs and pads used to adjust the body position. Materials used in body pressure-dispersion devices include air, water, urethane foam, gels and rubber.

Wound bed preparation: Management of the wound surface environment to promote wound healing. Specifically, necrotic tissue is removed, bacterial load is reduced, drying of the wound is prevented, excessive exudates are controlled, and pockets and wound edges are treated.

TIME: Practical principles of wound bed preparation based on the concept of evaluating factors that prevent wound healing from the viewpoints of tissue (T), infection or inflammation (I), moisture (M) and wound edge (E), and using the results for treatment and management

Moist wound healing: Maintaining the wound surface in a moist environment. This retains polynuclear leukocytes, macrophages, enzymes and cell growth factors contained in exudates on the wound surface. Such an environment promotes autolysis and removal of necrotic tissues, and does not interfere with cell migration.

Negative-pressure wound therapy (NPWT): A type of physical therapy. The wound is maintained in a closed environment and suction is applied to adjust the negative pressure of 125–150 mmHg. This therapy directly eliminates bacteria and exotoxins in the wound, promotes neovascularization in granulation tissue and alleviates edema.

Pocket: A wound cavity larger than a skin defect. The tissue covering a pocket is called the cover wall or cover lid. Undermine.

Washing: Removing chemical stimulants, infection sources and foreign bodies from the skin or wound surface using the pressure or lysing effect of a liquid. Washing may be performed using physiological saline, tap water or saline or tap water combined with a surfactant such as soap or detergent in a method known as washing with soap. The effect of washing may be derived from the flow volume or hydraulic pressure.

Debridement: A therapeutic action to clean the wound by removing foreign material, necrotic tissue, senescent cells that no longer react to stimulation by promoters of wound healing such as growth factors, as well as foci of bacterial infection, which are often associated with the above. Methods include: (i) autolytic debridement induced by occlusive dressing; (ii) mechanical debridement (e.g. wet-to-dry dressing, high-pressure washing, hydrotherapy and ultrasonic washing); (iii) debridement using proteolytic enzymes; (iv) surgical debridement; and (v) biological debridement using maggots.

Critical colonization: Conventionally, the microbial environment of the wound was classified into infected and aseptic states, but the current trend is to understand the two conditions as existing along a continuum (the concept of bacterial balance). Infection of the wound is understood as continuous stages of contamination, colonization and infection, and infection is considered to occur depending on the balance between the bacterial burden on the wound and host resistance. Critical colonization is a stage between colonization and infection when the balance has shifted toward infection and the number of bacteria has increased.

Biofilm: Bacteria that have colonized the surface of a foreign body or in necrotic tissue may produce polysaccharides on their body surface. These gradually fuse and form a membrane-like structure, which envelops bacteria. This is called a biofilm. Bacteria wrapped in a biofilm are protected from ordinary antibiotics and leukocytes, and so infection is likely to persist.

Seating: A supportive technique for using cushions and the like to provide a safe and comfortable seated position for the patient based on a physical evaluation taking into account the effect of gravity. It particularly refers to helping those patients who cannot sit upright to remain seated.

PREVENTION, CARE AND TREATMENT CONCEPTS, AND THE ALGORITHM FOR DIAGNOSIS AND TREATMENT

The basic principles for the prevention, care and treatment of pressure ulcers are to avoid compression and shearing forces to the skin and protecting the wound surface. When a pressure ulcer has developed, the principle of treatment is "wound bed preparation" based on the TIME concept in the early, "black" and "yellow" stages. Achieving the good wound bed in "red" and "white" stages, "moist wound healing" will be intended.

Note: The TIME concept is an acronym for "tissue" (treatment of non-viable or deficient tissue, that is management of necrotic/inactive tissue), "infection or inflammation" (control of infection or inflammation), "moisture" (correction of moisture imbalance, management of exudate) and "edge of wound" (treatment of non-advancing or undermined epidermal margin, management of the wound edge).

Figures 1 and 2 show "the algorithm for diagnosis and treatment of pressure ulcers", prepared based on the aforementioned concepts. The recommended and proposed treatments covered all the topical agents and dressing materials for injured skin, approved by the Japanese National Health Insurance Program, as well as surgical and physical treatments. While petroleum jerry-based antibiotic-containing ointments were approved for the treatment of erosion and ulcers by the Program, their use on deep pressure ulcers in the chronic phase may lead to the appearance of antibiotic-resistant bacterial strains; thus, the long-term use of those ointments should be avoided. Their use on the acute phase pressure ulcers or the chronic phase shallow ulcers, in expectation of the wound-protecting effects, is acceptable. So-called "wrap therapy", including open-moist therapy and other variations, not approved by the Japanese National Health Insurance Program, was also mentioned in this guideline, regarding the present situation that it is widely performed at home under the physician's supervision.

SUMMARY OF CLINICAL QUESTIONS

Table 2 indicates the CQ as well as the level of recommendation and description of the recommendation for each.

PRESSURE ULCER OR NOT
CQ1: HOW CAN A STAGE I PRESSURE ULCER BE DISTINGUISHED FROM REACTIVE HYPEREMIA?

Description of recommendation: Distinguishing using the transparent disk method (2C) or the finger compression method (2C) is proposed as an option.

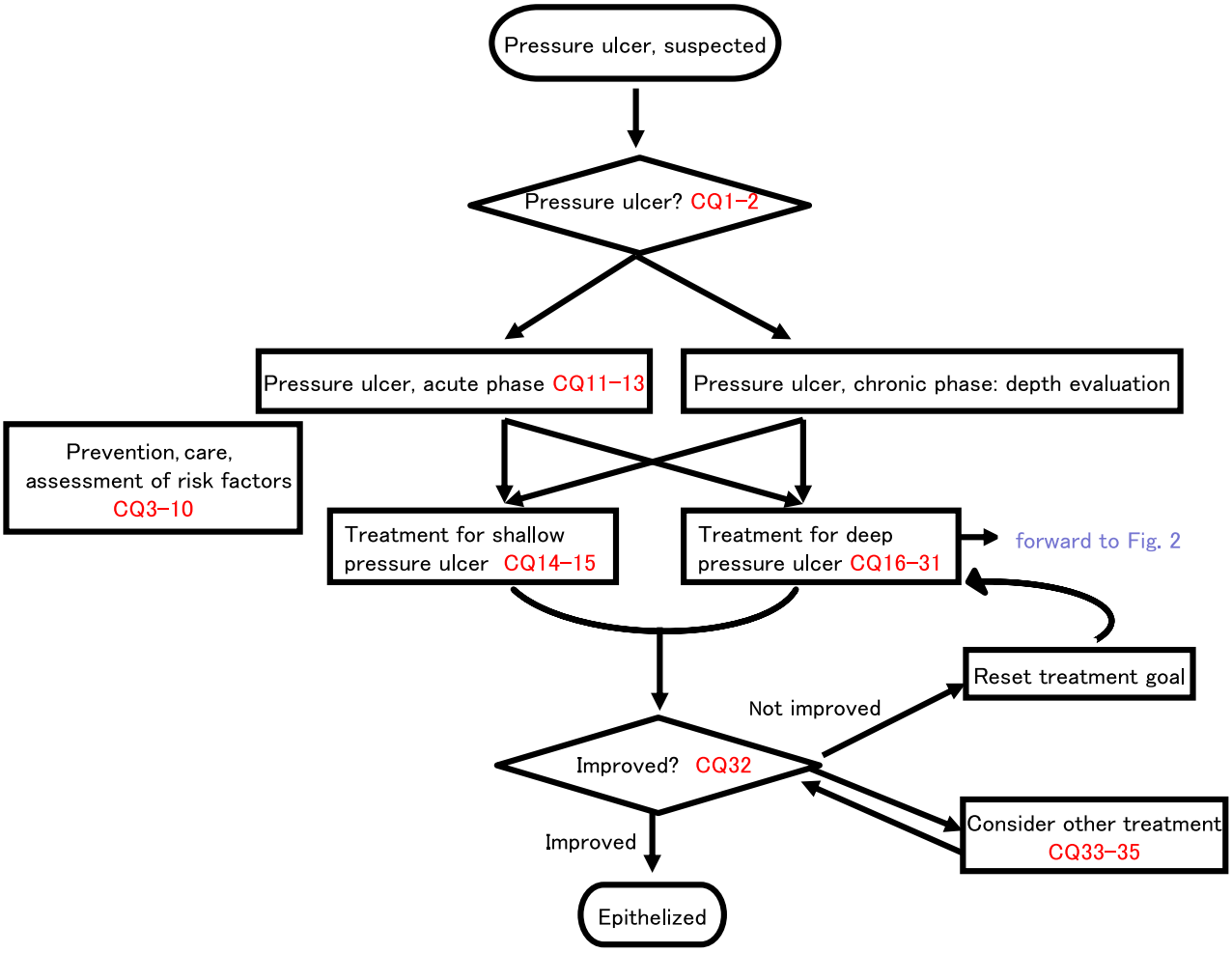

Figure 1. The Algorithm for diagnosis and treatment of pressure ulcers.

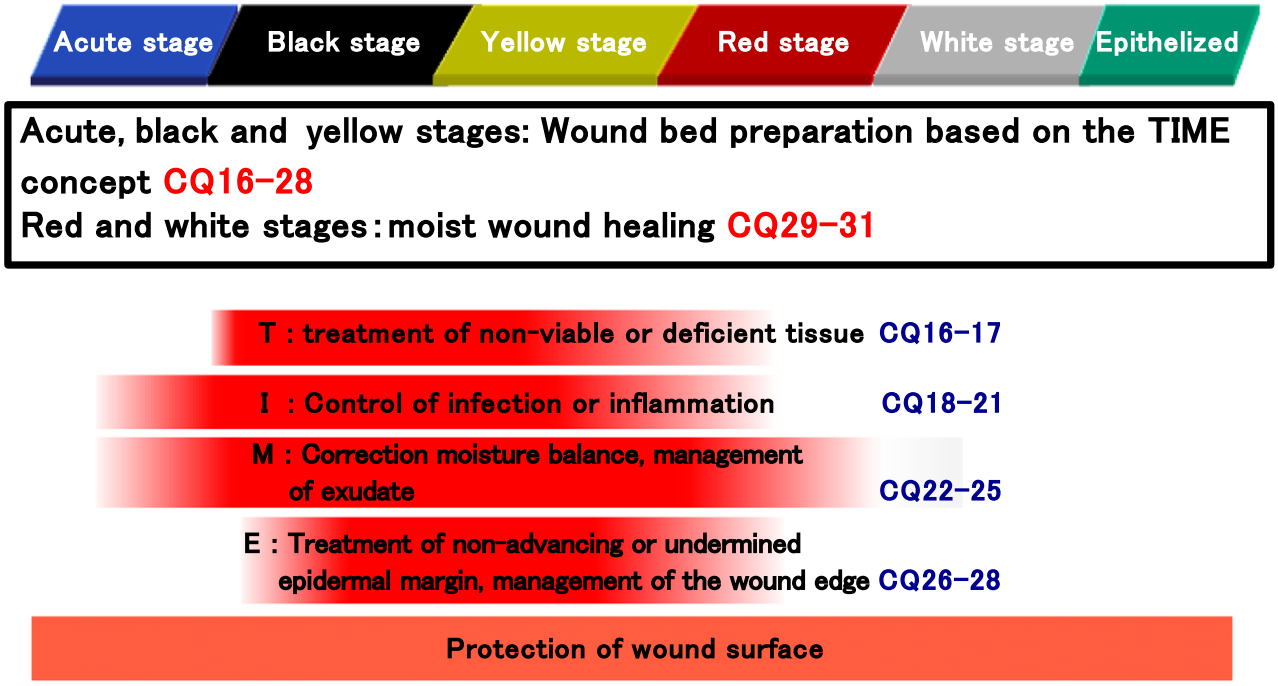

Figure 2. The Algorithm for treatment of chronic-phase deep pres sure ulcers (Modified from Tachibana T, Miyachi Y: The mechanism of pressure ulcer treatment, *Jpn J Cl in Nut r*. 2003; 103: 353–356).

Recommendation level: Transparent disk method, finger compression method (2C).

Commentary:

- There is a case–control study evaluating the relative superiority between the transparent disk method and the finger compression method for distinguishing between stage I pressure ulcers and reactive hyperemia,[1] and a case–control study evaluating whether there is a difference in the measured incidence of pressure ulcers depending on whether the method uses a finger for compression or a transparent plastic disk.[2] The evidence level for both is IVb and the recommendation level is 2C.
- In daily medical practise, either the transparent disk method or the finger compression method is used to distinguish between a stage I pressure ulcer and reactive hyperemia. Concerning which of these methods is preferable, there is a case–control study evaluating interrater reliability, degree of agreement (Cohen's kappa), sensitivity, specificity, positive predictive value and negative predictive value.[1] While the transparent disk method showed a slightly higher sensitivity, no significant difference was noted between the two methods, and so both are considered useful. In addition, when it was investigated whether a different incidence of pressure ulcer would be measured depending on whether the method used was the finger for compression or the transparent plastic disk method, the latter method was positive for a pressure ulcer in 3.9% of cases, while the incidence was 7.1% when using the finger compression method.[2] However, it is unknown which of these methods was more accurate.
- In addition, attempts to distinguish between the two tests by comparing blood flow using a laser Doppler technique,[3,4] skin temperature,[5] skin color using spectroscopy[6] and water content of the skin[7] have been made, but these did not achieve a significant discrimination of stage I pressure ulcer from reactive hyperemia.

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Table 2. Summary of clinical questions

Clinical question	Description of recommendation
(Pressure ulcer or not) CQ1: How can a stage I pressure ulcer be distinguished from reactive hyperemia?	Distinguishing using the transparent disk method (2C) or the finger compression method (2C) is proposed as an option. Recommendation level: Transparent disk method, finger compression method (2C).
CQ2: What are diseases that need to be distinguished from pressure ulcers?	The inclusion in differential diagnosis of reactive hyperemia, as well as peripheral arterial diseases due to diabetes, dermatitis due to irritation by stool or urine, cutaneous candidiasis, contact dermatitis, burns caused by an electric scalpel, and chemical burns due to disinfectants, is proposed. Recommendation level: 2C.
(Prevention, care, assessment of risk factors) CQ3: What scales are available for the assessment of risk factors?	Assessment scales for risk factors include the Braden Scale, K Scale, OH scale, K Scale modified for home use, and the pressure ulcer risk factor evaluation table presented by the Ministry of Health, Labor and Welfare. Their appropriate use is recommended. Recommendation level: 1A.
CQ4: What kind of skin care should be performed to prevent pressure ulcers?	The use of moisturizing creams (1A), and so forth, is recommended to protect the skin and to prevent pressure ulcers. In addition, the application of a polyurethane film (1A), polyurethane foam (1A), polyurethane foam/soft silicone (1A) or the like to bone protrusions for the prevention of pressure ulcers is recommended. Recommendation level: Moisturizing creams, polyurethane film, polyurethane foam, polyurethane foam/soft silicone (1A).
CQ5: Is nutritional support effective for the prevention and care of pressure ulcers?	Nutritional support (energy, protein) (1A) is recommended for the prevention and care of pressure ulcers. Supplementation of amino acids (1A), vitamins (1A) and trace elements (1A) is recommended. Recommendation level: Nutritional support (energy, protein), amino acids, vitamins, trace elements (1A).
CQ6: Are change in body position and body pressure dispersing devices useful for the prevention and care of pressure ulcers?	The use of a body pressure-dispersion mattress and periodic body position changes is recommended for the prevention of pressure ulcers (1A). For their care as well, the use of a body pressure-dispersion mattress and periodic body position changes is recommended (1A). Recommendation level: Prevention (1A). Care (1A).
CQ7: Can pressure ulcer patients bathe?	Bathing of patients with pressure ulcers is recommended. Recommendation level: 1C.
CQ8: What precautions are necessary when seating paraplegics or spinal cord injury patients with pressure ulcers in wheelchairs?	For wheelchair seating, checking body pressure is proposed for paraplegics and spinal cord injury patients with pressure ulcers. Recommendation level: 2C.
CQ9: Can the cure of pressure ulcers be promoted by improving the nutritional state?	To promote wound healing, prompt consultation with the nutrition support team or a specialist in nutritional guidance is recommended for patients with or at high risk of pressure ulcers and in a poor nutritional state. Recommendation level: 1A.
CQ10: How should pain in pressure ulcers be addressed?	The use of drugs such as anti-inflammatory analgesics and psychotropic drugs (2C), body pressure-dispersion beds (2C) and dressing materials (2C) is proposed as options for pain in pressure ulcers. Recommendation level: Anti-inflammatory analgesics and psychotropic drugs, body pressure-dispersion beds and dressing materials (2C).
(Pressure ulcers, acute phase) CQ11: What local treatments other than decompression should be performed for pressure ulcers in the acute phase?	If dressing materials are to be used in the acute phase, those that allow observation of the wound surface such as polyurethane film (1D) and hydrocolloids (1D) are recommended. If topical agents are to be used, oil-based ointments (1D) such as white petrolatum, zinc oxide, and dimethyl isopropyl azulene are recommended for protecting the wound surface, and silver sulfadiazine (1D) is recommended for preventing infection. For short-term use in the acute phase, ointments containing antibiotics (2D) are proposed as an option. Recommendation level: 1D, 2D. Polyurethane film, hydrocolloids, white petrolatum, zinc oxide, dimethyl isopropyl azulene and other oil-based ointments, silver sulfadiazine (1D). Ointments containing antibiotics (2D).

Table 2. (continued)

Clinical question	Description of recommendation
CQ12: What kind of examination should be performed if deep tissue injury is suspected?	For the diagnosis of deep tissue injury, imaging examinations (magnetic resonance imaging, ultrasound) and blood chemistry tests are proposed as an option. Recommendation level: 2C.
CQ13: What measures should be taken when deep tissue injury is suspected?	Careful observation of the systemic condition and course of the lesion with local decompression is recommended (1D). As local treatments, dressing of the wound surface using dressing materials that allow observation of the lesion such as a polyurethane film (1D) and translucent hydrocolloid dressings (1D) is recommended. Recommendation level: Careful observation of the systemic condition and course of the lesion with local decompression, polyurethane film, and translucent hydrocolloid dressings (1D).
(Shallow pressure ulcers)	For uninfected shallow pressure ulcers in the process of epithelization, the use of polyurethane film is proposed as an option.
CQ14: Is polyurethane film useful for the care of shallow pressure ulcers?	Recommendation level: 2D.
CQ15: What local treatments other than decompression should be performed for shallow pressure ulcers?	Protection of the wound while maintaining an appropriate moist environment is necessary for the cure of shallow pressure ulcers within the dermal level (erosion, shallow ulcers). Therefore, dressing materials often play a primary role in treatment. Hydrocolloids (1A), hydrogels (1B), polyurethane foam (1B) and chitin (1C) are recommended. If topical agents are used, white petrolatum, zinc oxide, dimethyl isopropyl azulene or another oil-based ointment (1D) is recommended for protecting the wound surface. For short-term use, ointments containing antibiotics (1D) and granulation-promoting drugs (1D), such as bucladesine sodium and prostaglandin E1, are recommended. Recommendation levels: 1A, 1B, 1C, 1D. Dressing materials: Hydrocolloids (1A). Hydrogels, polyurethane foam (1B). Chitin (1C). Topical agents: White petrolatum, zinc oxide, dimethyl isopropyl azulene, or other oil-based ointment, ointments containing antibiotics, granulation-promoting drugs such as bucladesine sodium and prostaglandin E1 (1D).
(Deep pressure ulcers)	Surgical debridement of necrotic tissue is recommended if the patient's overall condition would tolerate it, after the thorough evaluation of its indication. Recommendation level: 1D.
Treatment of early, "black" and "yellow" stage pressure ulcers: Wound bed preparation based on the TIME concept (CQ16–28)	
T: Treatment of non-viable or deficient tissue	
CQ16: Is surgical debridement useful for the removal of necrotic tissue?	
CQ17: What local treatments other than surgical debridement should be performed?	The use of cadexomer iodine (1A), dextranomer (1B), iodoform (1C) and bromelain (1D) is recommended for removing necrotic tissue from deep pressure ulcers. For dried necrotic tissue, the use of silver sulfadiazine (1D) is recommended. Among dressing materials, the use of hydrogels (1B) is recommended. Sufficient evidence is lacking for fradiomycin sulfate-crystalline trypsin (2D), and so we recommend not using it (at present). Wet-to-dry dressings (2B) also lack sufficient evidence, and so we recommend not using it (at present). Recommendation levels: 1A, 1B, 1C, 1D. Necrotic tissue at a deep pressure ulcer: Cadexomer iodine (1A). Dextranomer (1B) Iodoform (1C). Bromelain (1D). Dried necrotic tissue: Silver sulfadiazine (1D). Hydrogels (1B).

Table 2. (continued)

Clinical question	Description of recommendation
I: Control of infection or inflammation	It is recommended to diagnose the presence of infection by comprehensively evaluating local symptoms of the ulcer and surrounding skin, namely the four signs of inflammation (pain [1A], reddening [1D], swelling [1D], sensation of warmth [1D]), systemic symptoms such as fever (1D), results of bacteriological tests of the wound surface (1D) or the results of hematological and blood chemistry tests (1D). Recommendation levels: 1A, 1D. Pain (1A). Reddening, swelling, sensation of warmth, systemic symptoms such as fever, results of bacteriological tests of the wound surface, hematological and blood chemistry tests (1D).
CQ18: How should infection of pressure ulcers be diagnosed?	
CQ19: In what situations should antibiotics be administrated systemically?	Systemic administration of antibiotics is recommended not only when bacterial cultures from the ulcer surface are positive but also when signs of inflammation are noted in the skin surrounding the ulcer, or when fever, leukocytosis or exacerbation of the inflammatory reaction is observed. Recommendation level: 1D.
CQ20: What topical agents should be used as local treatments for controlling infection?	The use of cadexomer iodine (1A), silver sulfadiazine (1A), povidone-iodine sugar (1A), povidone-iodine gel (1C), iodine ointment (1D) and iodoform (1D) is recommended for controlling infection of pressure ulcers. As there is no sufficient evidence available for the use of an ointment containing an antibiotic (2A), we propose it not be used (at present). Recommendation levels: 1A, 1C, 1D. Cadexomer iodine, silver sulfadiazine, povidone-iodine sugar (1A). Povidone-iodine gel (1C). Iodine ointment, iodoform (1D).
CQ21: What dressing materials should be used as local treatments for controlling infection?	For dressing material when wound infection is localized, we recommend the use of silver-containing Hydrofiber® (1A), silver-containing polyurethane foam (1A) and silver-containing alginate (1A). Recommendation level: Silver-containing Hydrofiber, silver-containing polyurethane foam, silver-containing alginate (1A).
M: Correction of moisture imbalance, management of exudate	The use of cadexomer iodine (1A), dextranomer (1A), povidone-iodine sugar (1A), and iodine ointment (1D) is recommended in stages with excessive exudates. Recommendation levels: 1A, 1D.
CQ22: What topical agents should be used for local treatment of pressure ulcers during the black to yellow stages with excessive exudates?	Cadexomer iodine, dextranomer, povidone-iodine sugar (1A). Iodine ointment (1D).
CQ23: What dressing materials should be used for local treatment of pressure ulcers during the black to yellow stages with excessive exudates?	When there are excessive exudates, highly absorbent alginate (1A), polyurethane foam (including silver-containing preparations) (1A), chitin, Hydrofiber (including silver-containing preparations) (1C), Hydropolymer (1C) and polyurethane foam/soft silicone (1D) are recommended. Recommendation levels: Alginate, polyurethane foam (including silver-containing preparations) (1A). Chitin, Hydrofiber (including silver-containing preparations), Hydropolymer (1C). Polyurethane foam/soft silicone (1D).
CQ24: What topical agents should be used for local treatment of pressure ulcers during the black to yellow stages when exudate levels are low?	The use of silver sulfadiazine (1D), oil-based ointments (1D) such as white petrolatum, zinc oxide and dimethyl isopropyl azulene is recommended when exudate levels are low. Recommendation level: silver sulfadiazine, oil-based ointments such as white petrolatum, zinc oxide and dimethyl isopropyl azulene (1D).
CQ25: What dressing materials should be used for local treatment of pressure ulcers during the black to yellow stages when exudate levels are low?	The use of hydrogels (1B) is recommended when dried necrotic tissue has adhered to the wound and exudate levels are low. Recommendation level: 1B.

Table 2. (continued)

Clinical question	Description of recommendation
E: Treatment of non-advancing or undermined epidermal margin, management of the wound edge	For wound surfaces with high exudate levels in an undermining, the use of povidone-iodine sugar (1B) is recommended. If exudate levels are low, the use of trafermin (1C) or tretinoin tocoferil (1D) is recommended.
CQ26: What local treatments should be performed for undermined pressure ulcers?	However, if no improvement is observed with these treatments, surgical treatments or physical therapy should be evaluated. Recommendation levels: Povidone-iodine sugar (1B). Trafermin (1C). Tretinoin tocoferil (1D).
CQ27: How are undermined "pocket" pressure ulcers surgically cut open?	Surgical opening of undermined pressure ulcer, with appropriate bleeding control, is recommended. Whether to remove the overlying skin entirely should be determined on the individual patient's conditions. Recommendation level: 1C.
CQ28: Is negative-pressure wound therapy useful for undermined "pocket" pressure ulcers?	Negative-pressure wound therapy can be performed using either commercially available systems or handmade instruments. Both are recommended. Recommendation level: 1C.
Red and White stages: moist wound healing (CQ29–31)	The use of trafermin (1A), tretinoin tocoferil (1A), prostaglandin E1 (1A), lysozyme chloride (1B) and oil-based ointments (1D) such as calf blood extract, white petrolatum, zinc oxide, and dimethyl isopropyl azulene is recommended for wounds with appropriate to deficient exudates.
CQ29: What topical agents should be used for local treatment of pressure ulcers in the red to white stages?	The use of bucladesine sodium (1A), aluminum chlorohydroxy allantoinate (Alcloxa) (1B) and povidone-iodine sugar (1B) is recommended for wounds with excessive exudates or marked edema (B). Recommendation levels: Wound surfaces with appropriate to deficient exudates: Trafermin, tretinoin tocoferil, prostaglandin E1 (1A). Lysozyme chloride (1B). Oil-based ointments such as calf blood extract, white petrolatum, zinc oxide, and dimethyl isopropyl azulene (1D). Wound surfaces with excessive exudates or marked edema: Bucladesine sodium (1A). Aluminum chlorohydroxy allantoinate (Alcloxa), povidone-iodine sugar (1B).
CQ30: What dressing materials should be used for local treatment of pressure ulcers in the red to white stages?	The use of hydrocolloids (1A), hydrogels (1B), hydropolymer (1B), polyurethane foam (1B) and polyurethane foam/soft silicone (1B) is recommended for wound surfaces with appropriate to deficient exudates. The use of alginate (1C) or chitin (1C) is recommended for wound surfaces with excessive exudates or marked edema. Recommendation levels: Wound surfaces with appropriate to deficient exudates Hydrocolloids (1A). Hydrogels, hydropolymer, polyurethane foam, polyurethane foam/soft silicone (1B). Wound surfaces with excessive exudates or marked edema: Alginate, chitin (1C).
CQ31: Is negative-pressure wound therapy useful for the treatment of "red" stage pressure ulcers?	Negative-pressure wound therapy is recommended for stages III and IV pressure ulcers in "red" stage. Reconsideration is recommended for the indication on infected ulcers. Recommendation level: 1B.
(Are the pressure ulcers improved?)	The use of the DESIGN® (1C), DESIGN-R® (1C), the Pressure Ulcer Scale for Healing (PUSH) (1C) or the Pressure Sore Status Tool (PSST) (1C) is recommended for the assessment of pressure ulcers. Recommendation level: DESIGN, DESIGN-R, PUSH, PSST (1C).
CQ32: How should pressure ulcers be assessed?	
(Other treatment options)	Surgical treatment is recommended for pressure ulcers at stage III and above, but it should be performed after careful evaluation of the patient's general condition and indications. In addition, measures for infection control and surgical and/or chemical debridement should be performed in advance. Recommendation level: 1C.
CQ33: When should surgical treatments for wound closure be performed?	

Table 2. (continued)

Clinical question	Description of recommendation
CQ34: Can "wrap therapy" be used for pressure ulcers?	"Wrap therapy" is proposed as an option after having carefully considered the indications. However, as the user is liable for the use of material not approved for medical use such as kitchen cling film wrap, consent must be obtained from the patient and family before treatment. Recommendation level: 2B.
CQ35: What local treatments are performed other than surgical treatment and "wrap therapy"?	Hydrotherapy (1A), infrared-visual light therapy (1A), low-power laser therapy (1B) and hyperbaric oxygen therapy (1C) are recommended. In addition, ultraviolet therapy (2A) and electric stimulation therapy (2A) are proposed as options. Recommendation levels: Hydrotherapy, infrared-visual light therapy (1A). Low-power laser therapy (1B). Hyperbaric oxygen therapy (1C). Ultraviolet therapy, electric stimulation therapy (2A).

CQ2: WHAT ARE DISEASES THAT NEED TO BE DISTINGUISHED FROM PRESSURE ULCERS?

Recommendation description: The inclusion in the differential diagnosis of reactive hyperemia, as well as peripheral arterial diseases due to diabetes, dermatitis due to irritation by stool or urine, cutaneous candidiasis, contact dermatitis, burns caused by an electric scalpel and chemical burns due to disinfectants, is proposed.

Recommendation level: 2C.

Commentary:

- Although there is a case–control study evaluating how accurately a stage I pressure ulcer can be discriminated from reactive hyperemia,[8,9] the evidence concerning all other diseases consists of expert opinions.[10] Thus, the evidence levels are IVb and VI, respectively, and the recommendation level is 2C.
- Various conditions have been proposed needing differentiation from pressure ulcers. Reactive hyperemia is the most important, and the interrater reliability and degree of agreement were high when the diagnoses were made by those who underwent a certain level of training.[8,9] The next most important disease for differentiation is peripheral arterial disease (PAD) due to diabetes, previously known primarily as arteriosclerosis obliterans (ASO). Other diseases that need differentiation include dermatitis due to irritation by stool or urine, diaper dermatitis, cutaneous candidiasis, contact dermatitis, herpes zoster and bullous diseases.
- Among postoperative conditions, there are burns caused by electric scalpels and chemical burns due to disinfectants.[10] Burns due to electric scalpels have become quite rare in recent years. These are irregularly shaped, well-circumscribed erythema caused by electrical leakage. They occur immediately after surgery in areas such as lateral to, or above, the gluteal cleft. Chemical burns due to disinfectants are primarily irritant dermatitis caused by povidone-iodine and are well-circumscribed, irregularly shaped erythema occurring on surfaces in contact with sites adjacent to the disinfected area including the gluteal region. They are noted 3 days after disinfection in some patients, but can be detected immediately after surgery on close examination. Conversely, pressure ulcers are poorly circumscribed erythema occurring immediately after surgery or with a delay. The site, size and shape of the lesion are taken into consideration, but differentiation based on these characteristics is difficult, and so examination of the wound immediately after surgery assists with the diagnosis.[10]

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PREVENTION, CARE, ASSESSMENT OF RISK FACTORS

CQ3: WHAT SCALES ARE AVAILABLE FOR THE ASSESSMENT OF RISK FACTORS?

Recommendation description: Assessment scales for risk factors include the Braden Scale, K Scale, OH Scale, K Scale modified for home use, and the pressure ulcer risk factor evaluation table presented by the Ministry of Health, Labor and Welfare. Their appropriate use is recommended.

Recommendation level: 1A.

Commentary:

- There is a systematic review comparatively evaluating the predictive validity of multiple assessment scales.[11] The evidence level is I and the recommendation level is 1A. Also,

there is a prospective cohort study evaluating the validity of the K Scale regarding pressure ulcers in Japanese subjects, who show characteristics such as a low bodyweight and abnormal bone protrusion.[12] Similarly, there is a case–control study concerning the OH Scale[13] and a prospective cohort study regarding the K Scale modified for home use.[14] As for the pressure ulcer risk factor evaluation table prepared by the Ministry of Health, Labor and Welfare, there is a retrospective cohort study.[15]

- The Braden Scale, K Scale, OH Scale, K Scale modified for home use, and the pressure ulcer risk factor evaluation table released by the Ministry of Health, Labor and Welfare are the known assessment scales of risk factors. According to a systematic review comparatively evaluating the predictive validity of multiple assessment scales, the Braden Scale was superior to the Norton Scale, the Waterlow Scale and nurses' clinical judgment when the validity, sensitivity and specificity were assessed comprehensively.[11] However, Japanese patients, who are characterized by low bodyweight and abnormal bone protrusion, were not evaluated. Also, there is a study comparing the modified Braden Scale, Braden Scale and Norton Scale in Asian subjects, and reporting that the predictive validity was highest in the modified Braden Scale.[16] A meta-analysis of pediatric pressure ulcer assessment scales examined the Neonatal Skin Risk Assessment Scale for Predicting Skin Breakdown, Braden Q Scale, Burn Pressure Skin Risk Assessment Scale, Starkid Skin Scale and the Glamorgan Scale, but did not find any of these to be superior overall.[17] While these assessment scales for the prediction of the occurrence of pressure ulcers may contribute to more effective and efficient preventive measures against pressure ulcers, it remains unclear whether they significantly reduce the incidence of pressure ulcers.[18] In a systematic review of pressure ulcer prevention and assessment scales for risk factors, the Waterlow Scale did not result in a significant change in the incidence of pressure ulcers, and the Braden Scale and Norton Scale did not produce uniform results, and so the data are considered deficient.[19]
- Among studies in Japan, there is a prospective cohort study using the K Scale in bedridden patients,[12] a case–control study using the OH Scale,[13] and a retrospective cohort study using the pressure ulcer risk factor evaluation table of the Ministry of Health, Labor and Welfare, and each has been shown to be useful. Concerning elderly people residing at home, a prospective cohort study using the K Scale modified for home use, reported that the scale was considered useful in terms of sensitivity, specificity and so forth.

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CQ4: WHAT KIND OF SKIN CARE SHOULD BE PERFORMED TO PREVENT PRESSURE ULCERS?

Description of recommendation: The use of moisturizing creams (1A) and so forth is recommended to protect the skin and to prevent pressure ulcers. In addition, the application of a polyurethane film (1A), polyurethane foam (1A), polyurethane foam/soft silicone (1A) or the like to bone protrusions for the prevention of pressure ulcers is recommended.

Recommendation level: 1A.

Moisturizing creams, polyurethane film, polyurethane foam, polyurethane foam/soft silicone.

Commentary:

1. Regarding the protection of the skin by washing and prevention of pressure ulcers, there are five RCT using a squalene-containing cream or hyperoxygenated fatty acid compounds.[20–24] In addition, there are three RCT on prevention using polyurethane film[25–27] and two RCT on prevention using polyurethane foam.[28,29] The evidence level for each of these is II and the recommendation level is 1A.
2. As to whether or not skin care by washing or using a moisturizing cream is effective for the prevention of pressure ulcers, there have been five RCT using a squalene-containing cream or hyperoxygenated fatty acid compounds, and a significant preventive effect was observed in three RCT.[20–22] In addition, several reports have shown that the time until cure of pressure ulcers was shortened and the cure rate was improved using a skin protection agent in addition to skin cleansing.[30–32] However, the regimens and creams used vary among reports. In addition, many are not used in Japan, and it is unknown which specific component is the most effective.

3. There have been three RCT concerning prevention using polyurethane films, and each reported their usefulness.[25–27] When a polyurethane film was applied to bone protrusions in elderly patients, the incidence of both pressure ulcers[25] and persistent erythema[26] were significantly reduced. Also, by applying a polyurethane film to the sacral region to prevent the intraoperative onset of pressure ulcers, its incidence was significantly reduced.[27] In addition, there is an RCT showing a significant decrease in the incidence of pressure ulcers as a result of using a polyurethane film at the heel,[28] and an RCT showing a significant decrease in the incidence of pressure ulcers as a result of using polyurethane foam/soft silicone at the sacral region following cardiac surgery.[29]
4. Similarly, a report on adhering a hydropolymer to the heel with the objective of preventing intraoperative pressure ulcers also found a significant decrease in incidence.[33]
5. A polyurethane film is a film of polyurethane coated with a waterproof and hypoallergenic acrylic or vinyl ether adhesive, and it can seal and occlude wounds. Because it is transparent or translucent, the wound can be easily visualized. It is also waterproof and prevents the entry of water and bacteria, but nonetheless is semipermeable and allows the passage of gasses and vapor. Therefore, it not only maintains a moist environment for the wound, but it also does not interfere with perspiration or insensible water loss. For this reason, the skin around the wound does not become macerated, and so the barrier function of the skin remains intact. However, it should not be used for infected wounds, because a possibility has been noted that the bacteria in the resulting moist environment could proliferate rapidly.

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CQ5: IS NUTRITIONAL SUPPORT EFFECTIVE FOR THE PREVENTION AND CARE OF PRESSURE ULCERS?

Description of recommendation: Nutritional support (energy, protein) (1A) is recommended for the prevention and care of pressure ulcers. Supplementation of amino acids (1A), vitamins (1A) and trace elements (1A) is recommended.

Recommendation level: 1A.

Nutritional support (energy, protein), amino acids, vitamins and trace elements

Commentary:

- There are two meta-analyses concerning nutritional support (energy, protein) in patients with, and at risk of, pressure ulcers.[34,35] One meta-analysis[34] found nutritional support to be useful for prevention and treatment. The evidence level is I and the recommendation level is 1A.
- There are two meta-analyses concerning supplementation of amino acids, vitamins and trace elements.[34,35] This was recognized as useful for the prevention and care in one meta-analysis,[34] but not in the other.[35] There are also two RCT reporting the effectiveness of supplementation of amino acids, vitamins and trace elements for pressure ulcer care.[36,37] The evidence level is I and the recommendation level is 1A.
- A meta-analysis[34] shows that malnutrition is an important risk factor for pressure ulcers and that providing necessary nutrients (energy, protein) is effective for the management of pressure ulcer by preventing its occurrence in at-risk patients and promoting its cure in those who have developed it, and is recommended by guidelines in Japan, the USA and Europe.[38–40] In particular, supplementation of protein has been shown to be important for improving the wound condition.
- Because the resting energy expenditure is often elevated in pressure ulcer patients, it is necessary to supplement energy and protein to balance this expenditure. The energy demand is calculated by the formula: bodyweight × 25 (kcal) or basal

energy expenditure (calculated by the Harris–Benedict equation) × activity index × stress index (kcal). For the treatment of pressure ulcers, an activity index of 1.2–1.3 and a stress index of 1.2–1.3 are considered appropriate. In addition, a protein intake of 1.1–1.5 g/kg per day should be set as a target. For patients in whom intake of normal diet is insufficient or impossible, nutritional support using prescribable enteral nutrition products (L-6PM®, Elental®, Ensure Liquid®, Hepan ED®, Meibalance®, Renalen® and Isocal Plus EX®) should be considered.

- Harris–Benedict equation:
  Males: 66.5 + (13.8 × bodyweight) + (5.0 × height) − (6.8 × years age);
  Females: 655.1 + (9.6 × bodyweight) + (1.8 × height) − (4.7 × age).
- The nutritional state should be comprehensively evaluated based on body measurements, clinical findings and blood chemistry test results.
- Bodyweight is an index that reflects the nutritional state. The diagnosis of overweight or underweight should be made by calculating the body mass index (BMI) from the results of body measurements.

BMI = bodyweight (kg)/height (m^2) (a value of 22 is standard bodyweight; <18.5, underweight; and >25, overweight).

In addition, malnutrition is judged to be mild, moderate, and severe when the patient's bodyweight is 85–95%, 75–84% and 74% or less, respectively, of his/her usual bodyweight (determined by inquiry to the patient or his/her family). According to the rate of bodyweight change, malnutrition is considered possible if a loss of 2% or more in 1 week, 5% or more in 1 month, 7% or more in 3 months or 10% or more in 6 months is observed. The following indices should be referred to in estimating the body muscle and fat masses:

Triceps skinfold thickness (TSF): Measured using calipers at the midpoint between the acromion and ulnar head of the nondominant arm. Used to estimate the body fat mass.

Arm circumference (AC): Used to estimate muscle mass.

Arm muscle circumference (AMC: AC [cm] − π × TSF [mm] / 10): An index of the systemic muscle mass and lean bodyweight. Although it can be measured even in patients in whom body measurements are difficult due to marked contracture, it is important to take serial measurements and examine its changes, because of measurement errors.

- Subjective global assessment (SGA) is performed for clinical findings. SGA is an assessment method consisting of inquiries about both the history of disease (bodyweight changes, changes in food intake, gastrointestinal symptoms, physical function levels, disease and nutritional requirements) and physical examinations (fat mass, muscle mass, presence of edema). While it is a subjective scale of the nutritional state, it is difficult to use for beginners, as there is no scoring system. Therefore, if a patient is judged to have severe malnutrition, the NST or an expert in nutritional guidance should be consulted.
- Using blood chemistry testing, the nutritional state is evaluated primarily according to the ability of the liver to synthesize proteins. Chronic and acute nutritional states are reflected by proteins with long and short half-lives, respectively. Serum albumin has a long half-life of 21 days, and patients with a serum albumin level of 3.5 g/dL or lower are considered to be at risk of malnutrition. In elderly patients, however, the serum albumin level is often below this level, and so a threshold of 3.0 g/dL may be used. In chronic malnutrition, the serum albumin level may not decrease despite reductions in muscle mass and subcutaneous fat. Meanwhile, it has been reported that the nutritional state and serum albumin levels do not necessarily coincide, and so it is problematic as an indicator of nutritional state.[41] Serum transthyretin (prealbumin) has a short half-life of 2 days, and as it decreases markedly in acute malnutrition, it serves as an index of the current nutritional state. Malnutrition is possible when it is 17 mg/dL or less. In addition, a serum transferrin level of 200 mg/dL or less, serum cholesterol level of 150 mg/dL or less and total lymphocyte count of 1200/mm^3 or less may also serve as indices of malnutrition.[42,43]
- Regarding the administration of particular nutrients, there are RCT, despite the small number of patients enrolled, reporting that a significant difference in improvement in pressure ulcers was observed by the administration of nutrients involved in the wound healing process such as arginine, zinc and vitamin C.[36,37] Therefore, caution in preventing their deficiency is needed.[44] Arginine, which is a conditionally essential amino acid, promotes hydroxyproline synthesis and, thus, increases collagen synthesis and plays an important role in wound healing. Vitamin C, which is necessary in the process of conversion of procollagen into collagen, is also important for wound healing. Vitamin B1 is a coenzyme involved in cross-linking of collagen, and as its reserve in the body is small, it is prone to deficiency. Zinc is an important trace element located in the active centers of many metalloenzymes. Both its intake and content in the body decrease in elderly people, and its deficiency causes cutaneous and mucosal symptoms and delay of wound healing. Supplements of such nutrients available in Japan include Isocal/Arginaid®, Abound®, Protein Max®, V CRESC®, Tezon® and Enjoy Argina®. Liquid, gelatinous and other preparation types can be selected depending on swallowing capacity.

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CQ6: ARE CHANGES IN BODY POSITION AND BODY PRESSURE-DISPERSING DEVICES USEFUL FOR THE PREVENTION AND CARE OF PRESSURE ULCERS?

Description of recommendation: The use of a body pressure-dispersion mattress and periodic body position changes is recommended for the prevention of pressure ulcers. (1A).

For their care as well, the use of a body pressure-dispersion mattress and periodic changes in body position is recommended (1A).

Recommendation level: 1A.
Prevention (1A).
Care (1A).

Commentary:

- Systematic reviews[45–48] have shown that the incidence of pressure ulcers was reduced using a bodyweight-dispersion mattress and changing the body position compared with using a standard mattress or not changing the body position. The evidence level is I, and so the level of recommendation is 1A. A systematic review has also indicated their utility for care.[47] The evidence level is I, and so the level of recommendation is 1A. In addition, there is an RCT targeting wheelchair users.[49]
- Body pressure-dispersion mattresses can be classified by their specifications into those integrated with a bed frame (special beds), those that substitute a standard mattress (replacement mattresses) and those layered over a standard mattress (overlay mattresses). Functionally, also, they can be classified into mattresses that prevent high pressure from being applied to the same site for a long time by dynamically changing the air pressure, that is, the low-pressure-sustaining air mattress and those that statically deconcentrate the pressure. The latter includes urethane foam, gel, rubber and air pressure mattresses.
- Because bodyweight-dispersion mattresses can be selected using assessment tools appropriate for Japanese people such as the OH Scale, this assessment should be performed on inpatients upon admission. Generally, a low-pressure-sustaining air mattress should be selected prioritizing pressure dispersion for those who cannot roll over without assistance (independence level of life: C2), and a low-pressure-sustaining air mattress that resists sinking of the body, or a static body pressure-dispersion mattress prioritizing body position changes should be selected for those who can roll over alone (independence level of daily living: C1). A very large number of studies have been carried out to compare products, but no particular product has been consistently rated high.[45–48,50] Therefore, it is important to select a bodyweight-dispersion mattresses by taking the independence level, disease state, environment and social life of the patient into consideration. Also, for patients who have developed pressure ulcers, a static body pressure-dispersion mattress should be selected for those who can lie in a body position that causes no compression of the ulcerated area, but, as a rule, a pressure-adjustable body pressure-dispersion mattress should be selected for individuals who cannot lie in a position that causes no compression of the ulcerated area.[48]
- Generally, as pressure ulcers are considered unlikely to occur if the contact pressure is 40 mmHg or less, the contact pressure of the sacral region with a body pressure-dispersion mattress should be checked using a simple interface pressure meter. If a simple interface pressure meter is not available, the contact pressure of the low-pressure-sustaining air mattress should be checked using the bottom-touch method.[51] In the bottom-touch method, the appropriateness of the air cell pressure is evaluated by inserting the fingers with the palm up under the low-pressure-sustaining air mattress and flexing the second or third finger. The pressure is considered appropriate when the bone protrusion can be touched lightly with the finger flexed to a height of approximately 2.5 cm.
- Even with the use of an adjustable body pressure-dispersion mattress, the body position should be changed at appropriate intervals.[45–48] There is an RCT reporting that the incidence of pressure ulcers was higher when a pressure-adjustable body pressure-dispersion mattress was used without changing the body position than when a static type was used with body position changes,[52] but the results appear to depend on the characteristics of the mattress model as described below.
- The body position change interval is recommended to be within 2 h if tolerated by the physical conditions.[53] However, there are not only differences in function depending on the material and thickness of the static body pressure-dispersion mattress, but also qualitative differences in the pressure-adjusting function of the low-pressure-sustaining air mattress. In addition, low-pressure-sustaining air mattresses with an automated body position changing function (e.g. rolling function, multi-zone function) have been newly introduced. Therefore, it is difficult to discuss body pressure-dispersion mattresses in general, so there is presently no definite recommendation concerning the intervals of body position changes.

- For patients who have developed a pressure ulcer, a body position that minimizes compression of the ulcerated area should be selected. Relieving back strain when changing body position and applying the "rule of 30" when elevating the head of the bed are both useful measures for controlling friction and sliding of the patient. It is also important to pay attention to the condition of the mattress cover or sheet including avoidance of the hammock phenomenon (i.e. reduction in the effects of the body pressure-dispersion mattress by covering it with a bed sheet with excessive tension like a tent), the pressure setting of the low-pressure-sustaining air mattress (e.g. setting it at a level inappropriate for the patient's bodyweight), tube impaction and disconnection at coupled sections.[54]

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CQ7: CAN PRESSURE ULCER PATIENTS BATHE?

Description of recommendation: Bathing of patients with pressure ulcers is recommended.

Recommendation level: 1C.

Commentary:

- There is one study comparing cutaneous blood flow, bacterial load and pH before and after bathing,[55] and its evidence level is IVb. However, as bathing is essential for skin care and is widely practised in clinical settings, the recommendation level was set at 1C.
- Some textbooks describe bathing of pressure ulcer patients as being favorable, and there is a report indicating the effectiveness of bathing of elderly patients with pressure ulcers.[55] This report compares the cutaneous blood flow, bacterial load and pH before and after bathing in patients with pressure ulcers and shows a significant increase in the cutaneous blood flow and a significant decrease in the bacterial load after bathing. Also, there is a report that, when spinal cord injury patients with pressure ulcers were bathed, bacterial contamination of the bath tub derived more from the intestine than from the pressure ulcer and did not differ regardless of whether the pressure ulcer was dressed or not.[56] However, the effects of these findings on pressure ulcers are unknown.
- In bathing, it is considered useful to wash the skin particularly around pressure ulcers using soap.[57] In addition, while neutral or acid soap that is weakly degreasing is often used, there is no particular problem in using ordinary alkaline soap if it is gently foamed on the skin without rubbing it with a towel.[58]
- Although slightly different from bathing, footbaths are often used for the management of pressure ulcers on the heels. This has been reported to be useful[59] and the ulcer size was reportedly reduced significantly by bathing in a whirlpool bath.[60]

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CQ8: WHAT PRECAUTIONS ARE NECESSARY WHEN SEATING PARAPLEGICS OR SPINAL CORD INJURY PATIENTS WITH PRESSURE ULCERS IN WHEELCHAIRS?

Description of recommendation: Wheelchair seating and checking body pressure are proposed for paraplegics and spinal cord injury patients with pressure ulcers.

Recommendation level: 2C.

Commentary:

- There is one retrospective cohort study showing that attending a wheelchair seating clinic reduced the recurrence of pressure ulcers.[61] The evidence level is IVa and the recommendation level is 2C.

- In addition, there is one before/after study reporting that the tissue oxygen level recovered after alleviating compression using postural changes on a wheelchair,[62] and its evidence level is IVb. There is also a case report describing how pressure ulcers decreased by checking of the interface pressure in a wheelchair,[63] and the evidence level is V.
- Remaining in the same posture in a wheelchair for a prolonged period is considered to be a risk factor for pressure ulcers, but the recurrence of pressure ulcers decreased significantly when paraplegics and spinal cord injury patients were examined by a rehabilitation specialist and attended a seating clinic.[61] In addition, it has been reported that oxygen levels in compressed tissues recover if pressure can be relieved for approximately 2 min by changing the posture and elevating the body.[62] Other than lifting the body, anterior leaning of the body to 45° or more is effective, and approximately 70% of the pressure can be relieved in this body position.[64] There is also a report that pressure ulcers were reduced by having the interface pressure checked.[63]

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CQ9: CAN THE CURE OF PRESSURE ULCERS BE PROMOTED BY IMPROVING THE NUTRITIONAL STATE?

Description of recommendation: To promote wound healing, prompt consultation with the NST or a specialist in nutritional guidance is recommended for patients with or at high risk of pressure ulcers and in a poor nutritional state.

Recommendation level: 1A.

Commentary:

- There are two systematic reviews[65,66] concerning the administration of nutrition to pressure ulcer patients overseas, and one RCT concerning Japanese people. The evidence level is I and the recommendation level is 1A.
- There are three before/after studies comparing the postoperative incidence of pressure ulcers and the nutritional state before and after the introduction of NST.[68–70]
- Two systematic reviews[65,66] indicated that sufficient supplementation of protein and energy is effective for the prevention and treatment of pressure ulcers. There is an RCT indicating that the size of pressure ulcers decreased significantly as a result of a nutritional intervention for pressure ulcers in Japanese people.[67]
- In evaluating the nutritional state and planning nutrient administration, it is necessary to consult the NST or a specialist in nutritional guidance. Indeed, there is a report that the occurrence of pressure ulcers after gastrointestinal surgery was reduced ($P = 0.051$) by the introduction of NST, which is believed to have been due to shortening of the postoperative fasting period and an increase in the serum albumin level in the perioperative period.[68] There is study reporting that the incidence of pressure ulcers was reduced to approximately one-third after the introduction of NST.[69] Intervention by the NST or a specialist in nutritional guidance has been reported to be effective in not only the perioperative but also chronic phase,[70] although no relevant published work concerning the timing of such intervention is known.
- As indices for nutritional assessment, the serum albumin level (3.0–3.5 g/dL is a provisional criterion of malnutrition), bodyweight loss (a marked loss during the past 2 weeks and losses of 5% in 1 month, 7.5% in 3 months and 10% in 6 months are criteria for malnutrition) and eating rate (food intake rate: food intake of half the usual level or below over 2 weeks or longer is a criterion of malnutrition) are used.[71]
- The SGA tool is also frequently used by NST or specialists in nutritional guidance. The SGA consists of both an interview about disease history (bodyweight changes, changes in food intake, gastrointestinal symptoms, physical function levels, disease and nutritional demands) and physical examinations (fat mass, muscle mass, presence of edema) and aims to evaluate the subjective state of nutrition. However, it is difficult to use for beginners for reasons such as that the findings are not scored. Therefore, if a patient is judged to have severe malnutrition, consultation with the NST or a specialist in nutritional guidance is recommended.

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CQ10: HOW SHOULD PAIN IN PRESSURE ULCERS BE ADDRESSED?

Description of recommendation: The use of drugs such as anti-inflammatory analgesics and psychotropic drugs (2C), body pressure-dispersion beds (2C) and dressing materials (2C) is proposed as options for alleviating pain in pressure ulcers.

Recommendation level: 2C.

Anti-inflammatory analgesics and psychotropic drugs, body pressure-dispersion beds and dressing materials.

Commentary:

- There is a case–control study[72] and a case report[73] concerning the management of pain of pressure ulcers. The evidence level is IVb and the recommendation level is 2C. However, pain in pressure ulcers could be induced by infection and so this possibility must be ruled out.
- Of the patients with pressure ulcers, 37–66% were reported to have complained of pain at some point.[74] It has been reported that the intensity of pain is related to the depth of the pressure ulcer and that many patients felt pain during its treatment.[75]
- Anti-inflammatory analgesics, psychotropic drugs, anti-anxiety drugs and anesthetics are used to control pain. Although they are usually effective to an extent, they are often ineffective.[72,73] There is also a report that body pressure-dispersion bedding and dressing with a hydrocolloid (which alleviates pain as it maintains a moist environment without adhering to the wound and prevents exposure of denuded nerve terminals to air)[76,77] were effective for the control of pain.[72]
- Changing dressings can be a cause of pain.[78] Dressings that are less prone to causing pain include those made from soft silicone,[79] hydrogels, Hydrofiber® and alginate.[80]
- Even if there is a wound, no intense acute pain is caused without stimulation of nerve terminals (mechanical stimulation, chemical stimulation by neutrophil proteinases and complement) except early after its development. In addition, the effect of anti-inflammatory analgesics on chronic pain is limited (thus, the use of agents acting on the central nervous system, opioids or the like is considered). The cause of pain should be analyzed, and if it is related to local/systemic infection or nutritional state, management of these causes should be the priority.

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PRESSURE ULCERS IN THE ACUTE PHASE
CQ11: WHAT LOCAL TREATMENTS OTHER THAN DECOMPRESSION SHOULD BE PERFORMED FOR PRESSURE ULCERS IN THE ACUTE PHASE?

Description of recommendation: If dressing materials are to be used in the acute phase, those that allow observation of the wound surface such as polyurethane film (1D) and hydrocolloids (1D) are recommended. If topical agents are to be used, oil-based ointments (1D) such as white petrolatum, zinc oxide and dimethyl isopropyl azulene are recommended for protecting the wound surface, and silver sulfadiazine (1D) is recommended for preventing infection.

For short-term use in the acute phase, ointments containing antibiotics (2D) are proposed as an option.

Recommendation level: 1D, 2D.

Polyurethane film, hydrocolloids, white petrolatum, zinc oxide, dimethyl isopropyl azulene and other oil-based ointments, silver sulfadiazine (1D).

Ointments containing antibiotics (2D).

Commentary:

- There are no reports other than expert opinions concerning the selection of dressing materials and topical agents for the acute phase,[81–85] and the evidence level is VI. However, as the use of dressing materials and oil-based ointments for moist wound healing is an appropriate choice, and as they are used widely in clinical sittings, the recommendation level is 1D. The recommendation level for ointments containing antibiotics, which may lead to the development of resistant strains through long-term use, was set at 2D.
- Because pressure ulcers are unstable during the acute phase, the determination of the extent of necrosis is difficult, and the tissue's resistance to infection is weak. The discrimination between reactive hyperemia and stage I pressure ulcer is also difficult (see CQ1), and exacerbation in a short time is possible depending on the circumstances. Therefore, the objective of local treatment in this phase is to sufficiently observe the wound, protect it and prevent infection.

- Dressing materials are often used to protect the wound surface. However, as the condition changes rapidly in the acute phase, it is important to select dressing materials that allow observation of the wound. Also, as the wound and skin around it are vulnerable, the use of dressing materials that are only weakly adhesive is desirable.
- A polyurethane film is a film of polyurethane coated with a waterproof and hypoallergenic acrylic or vinyl ether adhesive and can seal/occlude the wound. Because it is transparent or translucent, the wound can be easily visualized. Also, as it is waterproof, it prevents the entry of water and bacteria, and as it is semipermeable, it allows the passage of gasses and vapor. Polyurethane film not only maintains a moist environment for the wound but also does not interfere with perspiration or insensible water loss. For this reason, it does not cause maceration of the skin around the wound and maintains the normal barrier function of the skin.
- Hydrocolloids retain moisture without adhering to the wound tightly, prevent crust formation as a result of wound drying, promote migration of epidermal cells by maintaining a moist wound environment and promote healing.[81] They also occlude the wound, prevent exposure of denuded nerve endings to air, and thus mitigate the characteristic tingling of shallow wounds.[82]
- Commercially available hydrocolloid materials, which are translucent and allow observation of the wound after application, include DuoACTIVE® ET. Also, Visiderm® (a translucent and waterproof polyurethane film using a hydrocolloid in the layer adhering to the skin) and Remois® Pad (a transparent polyurethane film having a three-layer structure with the layer adhering to the skin being a hydrocolloid compounded with moisture-retaining ceramide 2, a supportive layer above it that is a polyurethane film, and the outermost layer above it being a very slippery nylon knit with a low friction coefficient) may also be used, though they are not medical materials.
- When topical agents are used, a highly water-repellent oil-based ointment of white petrolatum, zinc oxide or dimethyl isopropyl azulene may be used to protect the wound surface.[83,84]
- If the prevention of infection is to be emphasized, silver sulfadiazine with an emulsion ointment having antibacterial activity and strong penetrating properties as the base should be used.[85] Because an oily base is used in ointments containing antibiotics such as gentamycin-containing ointment, they may be used for a short period to protect the wound surface and to control or prevent infection, but they must be used cautiously because of the possibility of developing resistant strains due to prolonged use.
- Silver sulfadiazine produces its infection-controlling effect on the wound surface due to the antibacterial activity of silver on the cell membrane and cell wall.[86,87] It controls the formation of biofilms of *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA).[88] Because of the emulsion base, it produces a debriding effect at the wound surface by causing softening and lysing of necrotic tissue. Its effect is attenuated when used concomitantly with povidone-iodine. Use of silver sulfadiazine in combination with other drugs, particularly enzymatic debriding agents, should be avoided.

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CQ12: WHAT KIND OF EXAMINATION SHOULD BE PERFORMED IF DEEP TISSUE INJURY IS SUSPECTED?

Description of recommendation: For the diagnosis of DTI, imaging examinations (magnetic resonance imaging [MRI], ultrasound) and blood chemistry tests are proposed as an option.

Recommendation level: 2C.

Commentary:

- There are currently only case reports concerning examinations for the diagnosis of DTI.[89–92] The evidence level is V and the recommendation level is 2C. In 2010, a descriptive systematic review of DTI was published, but the definition of DTI remains unclear, so it is considered that there is not a clearly effective method at present for its diagnosis and treatment.[93]
- DTI is a term used by the NPUAP in 2005 and refers to a pressure ulcer without epidermal loss (stage I) showing signs of damage to tissues deeper than subcutaneous tissue. In the NPUAP pressure ulcer staging revised in 2007, a new stage called (suspected) DTI was added.[94] However, pressure ulcers showing erosion (stage II) are also included in DTI if damage to tissues deeper than subcutaneous tissue is suspected. In addition, it is a name given to conditions in which an early diagnosis is difficult based on physical findings alone. What is the most important is to provide patient care with the possibility of DTI in mind.
- Diagnostic imaging is expected to support the diagnosis of deep lesions, but no methodology has been shown to date to be consistently useful for the diagnosis of DTI. There is

only a case report suggesting the possibility of predicting DTI by ultrasonography[89] and a case report in which deep injury could be visualized in an early stage by MRI, which can detect qualitative changes in muscles and soft tissues.[90]

- Diagnostic imaging may be useful for the differential diagnosis of pressure ulcers from other soft tissue infections (necrotizing fasciitis, gas gangrene, purulent myositis and osteomyelitis) and skin fistulas from retroperitoneal abscesses in elderly long-term bedridden patients. In addition, plain X rays of the wound area are useful for the differential diagnosis from gas gangrene (air images) and osteomyelitis.
- DTI may be accompanied by damage of muscle tissue, and there is a case report indicating elevation of the serum levels of muscle-derived enzymes (creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, myoglobin).[91] Therefore, a comprehensive evaluation including inflammatory reactions such as leukocytosis and C-reactive protein (CRP) and urinary myoglobin levels is necessary. In addition, DTI is often caused by prolonged surgery and sudden disturbance of consciousness, and detailed history taking may contribute to the diagnosis. Skin biopsy may be useful for the diagnosis because it may demonstrate necrosis of adipose tissue or sweat glands.

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CQ13: WHAT MEASURES SHOULD BE TAKEN WHEN DEEP TISSUE INJURY IS SUSPECTED?

Description of recommendation: Careful observation of the systemic condition and course of the lesion with local decompression is recommended (1D). As local treatments, dressing of the wound surface using dressing materials that allow observation of the lesion such as a polyurethane film (1D) and translucent hydrocolloid dressings (1D) is recommended.

Recommendation level: 1D.

Careful observation of the systemic condition and course of the lesion with local decompression, polyurethane film and translucent hydrocolloid dressings.

Commentary:

- There are only expert opinions about measures to take when DTI is diagnosed, and so the evidence level is VI. However, observing the progress of the wound surface is important so the recommendation level is 1D.
- DTI is a lesion accompanied by ischemic injury of muscle or soft tissue, and the estimation of the affected area as well as qualitative diagnosis is important. When DTI has been diagnosed, the patient should be placed in a body position to avoid compression of the lesion or, if it is impossible, the pressure on the lesion should be minimized using body pressure-dispersion devices.[95] Also, the possibility of exacerbation should be explained early to the patient and family while observing the skin surface (for bullae or purpura), carefully tracking serum muscle-derived enzyme levels, signs of inflammation and urinalysis results, and sufficiently managing infusions to avoid renal failure due to myoglobin.
- If there is pain, the possibility of inflammation of the ulcer base is high, and treatments including surgery should be evaluated in addition to symptomatic treatments such as non-steroidal anti-inflammatory drugs. If the pulse is felt and necrosis is noted in the epidermis, treatment should be initiated as described in CQ16.
- There are no reports evaluating the use of a polyurethane film or translucent hydrocolloid other than expert opinions, but maintaining a moist environment of the wound is expected to promote epithelial regeneration and wound healing. In addition, as nerve endings in pressure ulcers remain within the dermal level, exposure of these nerve endings to air has been reported to cause pain. This, however, can be alleviated by covering the wound surface with a dressing material.[96–98]
- A polyurethane film is a film of polyurethane coated with a waterproof and hypoallergenic acryl or vinyl ether adhesive and can seal or occlude wounds. Because it is transparent or translucent, the wound can be easily visualized. In addition, as it is waterproof, it prevents the entry of water and bacteria, but as it is semipermeable, it allows the passage of gasses and vapor. The polyurethane film not only maintains a moist environment of the wound but also does not interfere with perspiration or insensible water loss. For this reason, the skin around the wound does not become macerated, and the normal barrier function of the skin is maintained. However, caution is necessary, as it has been noted that if the wound is infected, bacteria could proliferate rapidly in the resulting moist environment.
- Hydrocolloids maintain a moist environment without adhering to the wound and prevent crust formation due to drying of the wound. They also promote migration of epidermal cells by maintaining a wet environment of the wound, thus accelerating healing.[97] They further occlude the wound, prevent exposure of denuded nerve endings to air, and thus reduce the characteristic tingling of shallow wounds.[98]

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SHALLOW PRESSURE ULCERS

CQ14: IS POLYURETHANE FILM USEFUL FOR THE CARE OF SHALLOW PRESSURE ULCERS?

Description of recommendation: For uninfected shallow pressure ulcers in the process of epithelization, the use of polyurethane film is proposed as an option.

Recommendation level: 2D.

Commentary:

- There are no reports evaluating the usefulness of a polyurethane film for the management of shallow pressure ulcers other than expert opinions. The evidence level is VI and the recommendation level is 2D.
- There are no reports evaluating the use of polyurethane film for shallow pressure ulcers at the dermal level (redness, bullae, erosion, shallow ulcers) other than expert opinions. If it is used for redness and bullae, it protects the wound from friction and sliding. In addition, if polyurethane film is used for erosion and shallow ulcers, it promotes epithelization and wound healing by maintaining a moist environment of the wound. Because nerve endings remain in pressure ulcers within the dermal level, exposure of denuded nerve endings to air has been reported to cause pain, but this pain may be alleviated by covering the wound surface with a film.[99]
- A polyurethane film is a film of polyurethane coated with a waterproof and hypoallergenic acrylic or vinyl ether adhesive and can seal or occlude wounds. Because polyurethane film is transparent or translucent, the wound can be easily visualized. In addition, as it is waterproof, it prevents the entry of water and bacteria, but as it is semipermeable, it allows the passage of gasses and water vapor. Polyurethane film not only maintains a moist environment of the wound but also does not interfere with perspiration or insensible water loss. For this reason, the skin around the wound does not become macerated, and the normal barrier function of the skin is maintained. However, caution is necessary, as it has been noted that if the wound is infected, bacteria could proliferate rapidly in the resulting moist environment.

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CQ15: WHAT LOCAL TREATMENTS OTHER THAN DECOMPRESSION SHOULD BE PERFORMED FOR SHALLOW PRESSURE ULCERS?

Description of recommendation: Protection of the wound while maintaining an appropriate moist environment is necessary for the cure of shallow pressure ulcers within the dermal level (erosion, shallow ulcers). Therefore, dressing materials often play a primary role in treatment. Hydrocolloids (1A), hydrogels (1B), polyurethane foam (1B) and chitin (1C) are recommended.

If topical agents are used, white petrolatum, zinc oxide, dimethyl isopropyl azulene or another oil-based ointment (1D) is recommended for protecting the wound surface. For short-term use, ointments containing antibiotics (1D) and granulation-promoting drugs (1D), such as bucladesine sodium and prostaglandin E1, are recommended.

Recommendation levels: 1A, 1B, 1C, 1D.

Dressing materials:

Hydrocolloids (1A).

Hydrogels, polyurethane foam (1B).

Chitin (1C).

Topical agents:

White petrolatum, zinc oxide, dimethyl isopropyl azulene or other oil-based ointment; ointments containing antibiotics, granulation-promoting drugs such as bucladesine sodium and prostaglandin E1 (1D).

Commentary:

- There are two RCT[100,101] and one systematic review[102] concerning local treatment for shallow pressure ulcers (erosion, shallow ulcer) using hydrocolloids. The evidence level is I and the recommendation level is 1A. While a significant difference was observed in the cure rate compared with saline gauze dressing, there was no significant difference compared with alginate, hydrogels or polyurethane foam.
- There are three RCT[103–105] using hydrogels, and so the evidence level is II. In comparison with saline gauze dressing,[103,104] hydrocolloids[104] and povidone-iodine,[105] there was no significant difference in cure rate found, so the recommendation level is 1B.
- There are five RCT using polyurethane foam,[106–110] and so the evidence level is II. In comparison with saline gauze + polyurethane film,[106] hydrocolloids,[107,108] hydrogels[109] and hydropolymer,[110] there was no significant difference in cure rate found, so the recommendation level is 1B.
- There is one case report using chitin.[111] The evidence level is IVb and the recommendation level is 1C. An epithelization effect has been reported with chitin.
- There are no papers concerning the use of topical agents for shallow pressure ulcers (erosion, shallow ulcer) other than expert opinions, and so the evidence level is VI. However, it would be appropriate to select an oil-based ointment with the objective of moist wound healing, and in addition, because such ointments are widely used in the clinical setting, the recommendation level was set at 1D. There are also only expert opinions for the use of granulation-promoting

drugs such as bucladesine sodium and prostaglandin E1, and so the evidence level is VI, but due to these being widely used in the clinical setting similarly to oil-based ointments, the recommendation level was set at 1D.

- Because it is necessary to protect the wound and maintain an appropriate moist environment for shallow pressure ulcers (erosion, shallow ulcers) within the dermal level, dressing materials are frequently used for their treatment. There are two RCT using hydrocolloids for shallow pressure ulcers.[100,101] No significant difference was observed in the cure rate compared with saline gauze dressing.[100] Compared with saline gauze dressing and phenytoin cream, the complete cure rate was significantly higher with hydrocolloids.[101] According to a systematic review summarizing these reports,[102] hydrocolloids were used primarily for EPUAP grades 2–3 pressure ulcers and were significantly superior to saline gauze dressing regarding the relative number of cured wounds, wound size reduction rate, time period in which the dressing must be changed, exudate-absorbing capacity, pain during dressing change, adverse effects and cost. Thus, hydrocolloids are considered to have advantages over saline gauze dressing in terms of efficacy and cost. However, hydrocolloids were inferior to alginate, hydrogels and polyurethane foam in the relative number of cured wounds, time until cure, wound size reduction rate, ease of handling, time period in which the dressing must be changed, exudate-absorbing capacity and pain during dressing change. Particularly, hydrocolloids were significantly inferior to alginate in the wound size reduction rate and pain during dressing change and to polyurethane foam in the time period after which the dressing must be changed, in the exudate-absorbing capacity and pain during dressing change. Concerning cost, hydrocolloids were more expensive than hydrogels or polyurethane foam. However, the differences in the efficacy compared with alginate, hydrogels or polyurethane foam was slight, and a clinical evaluation in a large number of patients is necessary. However, shallow pressure ulcers were not the only wounds evaluated in this review.
- Hydrocolloids maintain a moist environment without adhering to the wound and prevent crust formation resulting from drying of the wound. A moist environment of the wound promotes migration of epidermal cells and accelerates healing.[112] Moreover, hydrocolloids occlude the wound, prevent exposure of denuded nerve endings to air, and thus mitigate the characteristic tingling of shallow wounds.[113]
- There are three RCT on the use of hydrogels for shallow pressure ulcers.[103–105] No significant difference was observed in the cure rate compared with saline gauze dressings[103,104] or hydrocolloids.[104] Compared with povidone-iodine gauze dressing,[105] there was no significant difference in the wound size reduction rate, but epithelization was observed in 84% and 54% of the wounds dressed with a hydrogel and povidone-iodine gauze, respectively, which was a significant difference; thus, hydrogels are considered to promote healing by accelerating epithelization. However, shallow pressure ulcers were not the only target lesions in any of these trials. There is a case report regarding the use of hydrogels for shallow pressure ulcers[114] that reports its effectiveness for reducing wound area, pain and peripheral redness.
- Hydrogels not only promote granulation and epithelization by maintaining a moist environment, but these also alleviate pain by mitigating inflammation due to a rapid cooling effect.[115] Furthermore, being transparent, they allow easy visualization of the wound surface.[116]
- There are five RCT on the use of polyurethane foam for shallow pressure ulcers.[106–110] No significant difference was noted in the cure rate compared with saline gauze + polyurethane film[106] or hydrogels.[109] Compared with hydrocolloids, there was also no significant difference in the cure rate,[107,108] but polyurethane foam was significantly easier to remove[107,108] and leak-proof.[107] However, the time needed to change dressings was 12.3 min for polyurethane foam, which was significantly longer than the 7.6 min required for hydrocolloids.[107] Compared with hydropolymers,[110] there was no significant difference in the cure rate, but there was significantly less damage, maceration and residue at the skin around the wound with polyurethane foam. However, shallow pressure ulcers were not the only lesions evaluated in these trials.
- Polyurethane foam absorbs approximately 10 times its weight of exudates, maintains an appropriate moist environment, and promotes granulation and epithelization. It leaves no residues in the wound resulting from dissolution or detachment of the dressing material. In addition, as the surface that comes into contact with the wound is made of a non-adhesive polyurethane net, it is unlikely to rub off the newly formed epithelium even if it slides from the wound's surface.[115]
- There is one case series report describing the use of chitin for shallow pressure ulcers.[111] Of the 32 pressure ulcer patients, the lesions were within the papillary layer of the dermis in 11 patients. Chitin was also reported to show analgesic, exudate-controlling, granulation tissue-protecting and epithelization-promoting effects, and cure was observed in seven of the 11 patients. However, the chitin used was cotton-like chitin rather than unwoven chitin for wounds reaching the dermis.
- Chitin cotton is flexible, easy to apply to the wound surface and able to protect the wound.[111] It absorbs up to 25 times its weight in liquid.[117] It also promotes granulation, and the granulation tissue formed beneath is reddish and of high quality.[111] It can be used for astriction and hemostasis after debridement.[117]
- When topical agents are used, oil-based ointments, typically highly water-repellent white petrolatum, should be used for protecting the wound surface.[118] Oil-based zinc oxide and dimethyl isopropyl azulene ointments have the same effect and can be used for moist wound healing. In addition, granulation-promoting drugs, such as bucladesine sodium and prostaglandin E1, are recommended.
- Oil-based ointments containing antibiotics such as gentamycin-containing ointment may be used for a short period to protect the wound surface and control or prevent infection

for shallow pressure ulcers in the acute or chronic phases. However, caution is necessary due to the possibility developing resistant strains from long-term use.

- Many topical agents used for the treatment of skin ulcers fall into the category of granulation promoters, and most protect the wound surface or promote tissue repair and granulation by promoting the formation of matrix components (mucopolysaccharides) and fiber components (collagen) through fibroblast proliferation, by promoting angiogenesis or by improving local blood flow.[119]

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DEEP PRESSURE ULCERS

For deep pressure ulcers in stable condition beyond the acute phase, the treatment based on the "wound bed preparation", CQ16–28, and the "moist wound healing", CQ29–31, described below, is indicated. The ulcers located in peripheries of the limbs, such as the heels and toes, often caused by peripheral artery disease, for example, ASO. These ulcers may resemble pressure ulcers, but the pressure is a mere cofactor. Vascular surgery will be intended for healing the ulcers. Pressure ulcers on the ischial tuberosities among sensory neuropathy patients, such as spinal cord injuries, require appropriate seating in wheelchairs.

The indication of surgical treatment should be evaluated carefully, with attending physician, coworkers, other healthcare providers and the patient's family, when the patient's overall condition is poor, such as in end-stage malignancies, and wound healing is not predictable.

Treatment of early, "black" and "yellow" stage pressure ulcers: Wound bed preparation based on the TIME concept (CQ16–28).

T: TREATMENT OF NON-VIABLE OR DEFICIENT TISSUE
CQ16: IS SURGICAL DEBRIDEMENT USEFUL FOR THE REMOVAL OF NECROTIC TISSUE?

Description of recommendation: Surgical debridement of necrotic tissue is recommended if the patient's overall condition would tolerate it, after the thorough evaluation of its indication.

Recommendation level: 1D.

Commentary:

- The controlled trials on the usefulness of surgical debridement of necrotic tissue have not be published. However, debridement of necrotic tissue is essential for wound healing and its importance is emphasized in the EPUAP/NPUAP guideline[120] as an expert opinion. Evidence level is VI and recommendation level is 1D.
- Wound healing is not expected if necrotic tissue persists. Surgical debridement eliminates infection foci and promotes wound healing. It also contributes to the accurate evaluation of the wound.[120] Because the surgical debridement is an invasive procedure, it may lead the deterioration of the patient's overall condition; in an extreme condition, death may occur.[121,122] If surgical debridement is indicated in a thorough evaluation, the patient and his

family should be given a full explanation, and a written consent should be obtained before the debridement. In case the patient's condition does not allow the surgical debridement, sharp debridement, avoiding bleeding, may be indicated.

- It is important to check the patient's general condition preoperatively. Medications, such as antiplatelets and anticoagulants, require special attention. Guidelines for cardiovascular diseases recommended minor surgeries, in which hemorrhage can be controlled easily, to be performed without discontinuing these drugs.[123] Guidelines for cerebrovascular diseases recommended that oral warfarin should be continued, and that antiplatelet therapy can be continued.[124] The risk of hemorrhage should be evaluated in individual patients with attending physicians.
- In case there are apparent signs of infection, and the pressure ulcers are thought to be causing cellulitis, necrotizing fasciitis or sepsis, the emergent surgical debridement should be considered to save the patient's life, after obtaining the written consent from the patient and/or his families warning of the risk of hemorrhage and the expected prognosis unless debridement is performed. If not in urgent condition, autolysis may be promoted by topical agents or occlusive dressings. In this case, careful examination of the wound for the presence of infection is necessary, before occlusive dressings are performed.[120] Hydrosurgery devices for selective removal of necrotic tissue are approved by the Japanese National Health Insurance Programs under "wound debridement". The huge cost of disposable materials prevents the procedure from being commonly performed.
- The ulcers located in peripheries of the limbs, such as the heels and toes, often caused by peripheral artery disease, for example, ASO. In these ulcers, pressure is a mere cofactor, and the conventional treatment of pressure ulcer often fails. The indication for surgical debridement should be evaluated cautiously. If infection such as osteomyelitis is present, toes, foot or below-knee amputation may reduce the physical stress on the patient.

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CQ17: WHAT LOCAL TREATMENTS OTHER THAN SURGICAL DEBRIDEMENT SHOULD BE PERFORMED?

Description of recommendation: The use of cadexomer iodine (1A), dextranomer (1B), iodoform (1C) and bromelain (1D) is recommended for removing necrotic tissue from deep pressure ulcers.

For dried necrotic tissue, the use of silver sulfadiazine (1D) is recommended. Among dressing materials, the use of hydrogels (1B) is recommended.

Sufficient evidence is lacking for fradiomycin sulfate-crystalline trypsin (2D), and so we recommend not using it (at present). Wet-to-dry dressings (2B) also lack sufficient evidence, and so we recommend not using it (at present).

Recommendation levels: 1A, 1B, 1C, 1D.

Necrotic tissue at a deep pressure ulcer:
Cadexomer iodine (1A).
Dextranomer (1B).
Iodoform (1C).
Bromelain (1D).

Dried necrotic tissue:
Silver sulfadiazine (1D).
Hydrogels (1B).

Commentary:

- There are three non-blinded RCT on the debriding effect of cadexomer iodine,[125–127] and so the evidence level is II. It was shown to be superior to a fibrinolysin-DNase mixture[126] and so the recommendation level is 1A.
- There is one non-blinded RCT on the debriding effect of dextranomer,[128] and so the evidence level is II. However, no significant difference has been found compared with physiological saline dressings. In addition, a non-randomized, uncontrolled comparison study (evidence level III)[129–131] found an improvement, so the recommendation level is 1B.
- There is one case–control study on the debriding effects of iodoform.[132] The evidence level is IVb and the recommendation level is 1C.
- There is one RCT on the debriding effect of bromelain, but it does not consider pressure ulcers.[133] There are only expert opinions about pressure ulcers. Thus, the evidence level is VI and the recommendation level is 1D.
- There are only expert opinions on the debriding effect of silver sulfadiazine,[134,135] and so the evidence level is VI. The use of an emulsion-based ointment is an appropriate choice for eliminating necrotic material, and as it is widely used in the clinical setting, the recommendation level is 1D.
- There is one RCT on the debriding effect of using hydrogels on pressure ulcer patients with necrotic tissue.[136] The evidence level is II, but no significant difference was found in the rate of necrotic tissue elimination compared with the dextranomer, so the recommendation level is 1B.
- Concerning fradiomycin sulfate-crystalline trypsin, there are expert opinions about removal of necrotic tissue, but the recommendation level was set at 2D because of the possibility of the development of resistant strains on long-term

use. There are two non-blinded RCT concerning the debriding effect of wet-to-dry dressing,[137,138] but no significant difference was noted in time until cure in either report. In addition, as the treatment is costly and time-consuming, its economic efficiency is questionable, and so the recommendation level was set at 2B.

- The removal of necrotic tissue can be accelerated and promoted by combining surgical debridement with other treatments including topical agents depending on the condition of the wound. In addition, if surgical debridement is impossible due to a poor general condition of the patient, debridement using topical agents is often selected. Debridement using topical agents includes chemical debridement by enzyme preparations and induction of autolysis by maintaining an appropriate moist environment.
- There are three non-blinded RCT concerning the debriding effect of cadexomer iodine.[125–127] No significant difference was noted in the studies comparing the treatment with dextranomer or the base material, dextrin polymer,[125,127] but cadexomer iodine was significantly superior in reducing eschar (dried and hardened necrotic tissue) after a 4- and 6-week treatment in a study comparing it with a drug containing fibrinolysin-DNase.[126]
- Cadexomer iodine produces a bactericidal effect by slowly releasing iodine.[139] Dextrin polymer also absorbs not only exudates but also bacteria.[139–141] Therefore, it is useful for the treatment of wounds with a large amount of exudates or pus, but careful washing is necessary so as not to leave behind old polymer beads when changing the dressing; thus, it should not be used in patients with undermined ulcers that are difficult to clean.[134] Insufficient exudate leads the dried wound surface, and the wound healing may be prolonged. During the active granulation stage, iodine can inhibit granulation tissue. In addition, caution is needed with respect to iodine allergies.[134]
- There is one non-blinded RCT on the debriding effect of dextranomer.[128] The rate of improvement using dextranomer was 80%, but was 13% with the use of physiological saline dressings. However, there was no significant difference between them. In addition, there are three non-randomized uncontrolled comparison studies[129–131] that variably report that the rate of improvement of necrotic tissue after 4 weeks was 91.3% in three of eight pressure ulcers,[129] that the rate of improvement after 4 weeks was 84.1% in 93 cases of skin ulcer including 25 pressure ulcers[130] and that four cases of copious necrotic tissue had decreased to one case after 1 week.[131]
- Dextranomer is reported to clean the wound surface by absorbing exudates.[142] In addition to absorbing exudates, it also eliminates bacteria.[143] Currently available are powdered preparations and paste preparations compounded with macrogol and purified water, which are used as National Health Insurance medical materials. Because the preparations are water-absorbing, they are favorably indicated for patients with excessive/appropriate exudates, and caution is necessary to avoid drying of the wound surface.
- Regarding the debriding effect of the proteolytic enzyme bromelain, there is one double-blind RCT.[132] A significant improvement compared with an inactivated placebo was reported, but the trial was targeted to burn injuries, and pressure ulcers were not included. In terms of studies on pressure ulcers, there are two non-randomized uncontrolled comparison studies.[144,145] At least a mild debriding effect was observed in 14 of 16 patients (88%) in one of these studies, and in 10 of 11 patients (91%) in the other.
- When using bromelain, caution for the frequent occurrence of pain is necessary. The normal skin around the ulcer must be protected with oil-based ointments.[134] In addition, as highly water-absorbing macrogol is used as the base, caution for attenuation of the debriding effect is necessary when exudates or wetness of the wound decreases.[134]
- There is one case–control study reporting the debriding effect of iodoform,[133] identifying patients with necrotic tissue in a 2-year period. Comparing the rate of necrotic tissue elimination in 30 patients treated with iodoform gauze and 30 treated with an ordinary topical treatment (silver sulfadiazine, povidone-iodine sugar), iodoform gauze was significantly superior in all observation timeframes from 1 to 4 weeks after the start of treatment.
- Iodoform is used as an antiseptic dressing material contained within gauze. Iodoform exerts a bactericidal effect by being dissolved in bodily fluids and releasing iodine. It exhibits odor control and secretion control effects, and is mildly analgesic as well.[146] Of note, it also has a debriding effect and, thus, is easily used for debridement when infection is present. It is commonly used for cleaning the inside of undermining, but large-scale use has caused symptoms of poisoning,[147] and caution is needed with respect to iodine allergies.[148]
- Silver sulfadiazine is frequently used for dried necrotic tissue to induce autolysis, but there are only expert opinions discussing its use for removing necrotic tissue.[134,135]
- Because silver sulfadiazine is prepared with an emulsion base with a high water content, it is frequently used for dried necrotic tissue to induce its autolysis.[135] Caution is necessary as it may induce edema of the wound surface if exudates are abundant.[134] The effectiveness of silver sulfadiazine is attenuated when used with povidone-iodine. Its use with other drugs, particularly, external enzyme preparations, should be avoided.[133,134]
- There is one RCT concerning the debriding effect of hydrogels in pressure ulcer patients with necrotic tissue.[136] Compared with dextranomer, the wound size reduction rate on the 21st day was significantly greater with hydrogels, but no significant difference was noted in the necrotic tissue removal rate between the two materials.
- Hydrogels not only absorb and retain exudates from the wound, but, because hydrogels themselves contain water, they also soften the wound and necrotic tissue, accelerating its removal.[149] Also, hydrogels do not cause pain or reddening/inflammation of the surrounding intact skin as is observed in chemical debridement using enzyme

preparations.[150] If necrotic tissue is found to be macerated when the dressing is changed, surgical debridement should also be performed to the extent possible.[150]

- There are no papers concerning the debriding effect of fradiomycin sulfate-crystalline trypsin other than expert opinions.
- Fradiomycin sulfate-crystalline trypsin is an external powdered preparation obtained by compounding the antibiotic fradiomycin sulfate and the proteolytic enzyme trypsin, which has a necrotic tissue-lysing effect. By combining the two agents, the cleansing of the wound and the chemical debridement effect resulting from the proteolytic enzyme promote the penetration of the wound by the antibiotic, stimulating the wound healing mechanism.[151] However, when an ointment containing an antibiotic is applied to deep pressure ulcers for infection control, it is used for an extended period of time, which can lead to microbial substitution (see CQ20).
- Concerning the debriding effect of wet-to-dry dressing, there are two non-blinded RCT.[137,138] In comparison with hydrocolloids used in 44 pressure ulcer patients, there was no significant difference in the cure rate or cure speed, and in fact hydrocolloids exhibited a faster result. In addition, the time until cure was markedly longer, and the cost was significantly higher when wet-to-dry dressing was used.[137] When compared with an original sustained negative-pressure therapy as well, the time until wound closure did not differ significantly; moreover, the cost was higher for wet-to-dry dressing.[138]
- Wet-to-dry dressing, performed by applying gauze saturated with saline to the wound surface and non-selectively removing foreign material and necrotic tissue adhering to the gauze once it has dried when the dressing is changed, is employed for debridement. Although it has been used for centuries and can be performed readily using gauze and saline that are always available at any medical facility, its drawbacks such as pain when changing the dressing, necessity of 2–3 daily dressing changes, maceration of the surrounding normal skin due to excessive moistening of the wound, possibility of entry of external contaminants into the wound and detachment of newly formed granulation tissue with removal of dried gauze have been reported.[152,153]

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I: CONTROL/ELIMINATION OF INFECTION
CQ18: HOW SHOULD INFECTION OF PRESSURE ULCERS BE DIAGNOSED?

Description of recommendation: It is recommended to diagnose the presence of infection by comprehensively evaluating local symptoms on the surface of the ulcer and surrounding skin (physical findings), namely the four signs of inflammation (pain [1A], reddening [1D], swelling [1D], sensation of warmth [1D]), systemic symptoms such as fever (1D), results of bacteriological tests of the wound surface (1D) or the results of hematological and blood chemistry tests (1D).

Recommendation levels: 1A, 1D.

Pain (1A).

Reddening, swelling, sensation of warmth, systemic symptoms such as fever, results of bacteriological tests of the wound surface, hematological and blood chemistry tests (1D).

Commentary:

- A meta-analysis regarding infection of pressure ulcers combining 15 studies and 985 patients evaluated diagnosis based on the clinical condition,[154] and so the evidence level is I. According to this study, the positive likelihood ratio for pain as a predictor of infection was high at 11–20, which was significant. The evidence level is I and the recommendation level is 1A. However, aside from pain, no other clinical symptoms or test values were identified that could significantly predict the presence of infection. Aside from this report, there are only expert opinions[155] with an evidence level of VI, but in the actual clinical setting, there are patients who do not complain of pain despite the presence of infection, and so it is necessary to diagnose infection through a comprehensive view of clinical symptoms and test data. Thus, the recommendation level was set at 1D.
- Infection should be diagnosed on the basis of findings such as reddening, swelling, tenderness, pus discharge, an increase in exudate, and unpleasant odor on the ulcer surface and surrounding skin.[155] Usually, some bacteria are attached to the surface of the pressure ulcer but they do not cause infection. The concept of bacterial balance, namely understanding the bacterial state of the wound along a continuum that includes contamination, colonization and infection, where infection occurs depending on the balance between the bacterial burden to the wound and the resistance of the body, has recently become mainstream, replacing the conventional view of either an aseptic or infected state.[156] There is also the stage of critical colonization, which is a state occurring between colonization and infection, when the balance between the two shifts toward infection as the bacteria count increases stemming from the state of colonization. A specific example occurs when no improvement, for example, a decrease in the wound size or epithelialization, is observed after 2 weeks.[157]
- Examination and evaluation of the wound provide important information for the diagnosis of infection.[158] Once infection occurs, pulsations may be felt below the black necrotic tissue, fine granular granulation tissue may enlarge into large edematous nodules, the color of granulation tissue may change from clear red to a darker color or the surface may become sticky. Alternately, exudate increases and becomes pus-filled or viscous in the event of infection, but decreases and returns to slightly bloody or serous with its suppression.
- If infection is accompanied by systemic symptoms, such as fever, it is also necessary to measure inflammation indicators such as the peripheral white blood cell count and CRP. If the body temperature is high, sepsis should be suspected and a blood culture should be performed. In the event of infection, the causative microorganism must be identified by culturing, and susceptibility tests must be performed simultaneously. Resident bacteria such as *Staphylococcus epidermidis* are detected frequently from shallow pressure ulcers, but mixed infections of *S. aureus*, *Streptococcus pyogenes* or *Pseudomonas aeruginosa* with *Escherichia coli*, enterococci or *Proteus vulgaris* are often observed in deep pressure ulcers.[157,158]
- If exudates are abundant with an intensely poor odor, an abscess under the wound should be suspected, and incision and drainage should be performed. However, prior to such a procedure, the patient's general condition, blood test results (cell counts, clotting factors), and medications such as antiplatelet agents and anticoagulants should be checked. According to the guidelines regarding cardiovascular diseases, the continuation of such medications is recommended for minor surgery, in which bleeding can be readily controlled.[159] Guidelines for cerebral infarction also mention that "oral administration of" warfarin "is desirable" and that antiplatelet therapy "may be continued".[160] However, as these medications can be suspended in some patients, it is desirable to first consult with the attending physician and to manage patients individually. If bleeding at home is expected to result from treatment, the patient should be referred to a facility capable of appropriate treatment.
- Soft tissue infections are often detected due to a complaint of pain. However, as many patients with spinal cord injury are desensitized and do not complain of pain, infection is likely to be exacerbated,[161] and so special attention is needed. In addition, if there is infection, careful selection of topical agents is necessary (see CQ20).

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CQ19: IN WHAT SITUATIONS SHOULD ANTIBIOTICS BE ADMINISTRATED SYSTEMICALLY?

Description of recommendation: Systemic administration of antibiotics is recommended not only when bacterial cultures from the ulcer surface are positive but also when signs of inflammation are noted in the skin surrounding the ulcer, or when fever, leukocytosis or exacerbation of the inflammatory reaction is observed.

Recommendation level: 1D.

Commentary:

- There is no report on the effects of systemic administration of antibiotics for infection of pressure ulcers except an expert opinion,[162] and so the evidence level is VI. However, given it is essential to control wound infection, and systemic administration is widely performed in clinical settings, the recommendation level was set at 1D.
- Contamination of wounds in general should be managed first by thorough lavage with physiological saline, and surgical debridement should be performed if necrotic tissue is observed. If signs of inflammation such as reddening, swelling, fever and pain are still observed on the ulcer surface or the surrounding skin, systemic administration of antibiotics should be considered.[162] Infections derived from pressure ulcers include cellulitis, fasciitis, osteomyelitis and sepsis, and systemic administration of antibiotics should be promptly initiated if systemic symptoms suggestive of these conditions such as fever, leukocytosis and elevated CRP levels are observed.[162,163] Systemic administration of antibiotics should also be initiated promptly if a pressure ulcer patient has developed infection in areas other than the pressure ulcer such as the urinary tract, cardiac valves and paranasal sinus.[162]
- If there are signs of systemic or local infection, a second-generation cephalosporin antibiotic should be selected until the results of bacterial culture become available. Once the causative bacteria are identified, it is important to select agents with limited spectrum based on antibiogram results of antibiotic sensitivity testing. If antibiotics are not effective, their use should not be continued aimlessly, but rather the causative microorganisms and their foci (e.g. is there an abscess below the ulcer, is there sepsis) should be reevaluated. If an MRSA infection is suspected, the drug should be promptly changed to an anti-MRSA drug. Resident bacteria such as *S. epidermidis* are detected frequently from shallow pressure ulcers, but mixed infections of *S. aureus*, *S. pyogenes* or *P. aeruginosa* with *E. coli*, enterococci or *P. vulgaris* are often observed in deep pressure ulcers.[164]
- The odor of the wound and color of exudates attached to gauze are informative for inferring the causative microorganisms of infected pressure ulcers.[164] For example, lesions appear grayish white when infected by *S. epidermidis*, yellowish green when infected by *S. aureus* and greenish blue with a sweet–sour odor when infected by *P. aeruginosa*. Mixed infection with anaerobic bacteria causes a brownish color and a foul odor.
- Patients with pressure ulcers are likely to become carriers. If resistant microorganisms such as MRSA, multidrug-resistant *P. aeruginosa* and multidrug-resistant *Acinetobacter* are detected, a gown, mask, cap and gloves should be worn to prevent nosocomial infection. In addition, all tools used should be converted to disposable ones, and surveillance cultures should be performed.[163]

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CQ20: WHAT TOPICAL AGENTS SHOULD BE USED AS LOCAL TREATMENTS FOR CONTROLLING INFECTION?

Description of recommendation: The use of cadexomer iodine (1A), silver sulfadiazine (1A), povidone-iodine sugar (1A), povidone-iodine gel (1C), iodine ointment (1D) and iodoform (1D) is recommended for controlling infection of pressure ulcers.

As there is no sufficient evidence available for the use of an ointment containing an antibiotic (2A), we propose it not be used (at present).

Recommendation levels: 1A, 1C, 1D.

Cadexomer iodine, silver sulfadiazine, povidone-iodine sugar (1A).

Povidone-iodine gel (1C).

Iodine ointment, iodoform (1D).

Commentary:

- There are three RCT concerning infection control, each with cadexomer iodine, silver sulfadiazine and povidone-iodine sugar,[165–173] and so the evidence level is II for each of these. Cadexomer iodine has been shown to be superior in a comparison against dextranomer and a base of dextrin polymer, and so the recommendation level is 1A. Silver sulfadiazine has been shown to be superior in a comparison against povidone-iodine solution and a base, and so the recommendation level is 1A. Povidone-iodine sugar has been shown to be superior in a comparison against sucrose and calf blood extract, and so the recommendation level is 1A.
- There is one case report concerning povidone-iodine gel,[174] and so the evidence level is V. The report was of an effective case, and so the recommendation level is 1C.
- There is no published work concerning infection control with iodoform or iodine ointment other than expert opinions,[175,176] and so the evidence level is VI. These are effective drugs for controlling infection and are widely used in the clinical setting, and so the recommendation level is 1D.
- There are two RCT concerning infection control using ointments containing antibiotics or antibacterial drugs,[166,170] and so the evidence level is II, but neither study showed such treatment to be superior. In addition, as ointments containing antibiotics or antibacterial drugs are often used for extended periods for deep pressure ulcers in the chronic phase, which is likely to invite microbial substitution, the recommendation level was set at 2A.
- There are three RCT concerning infection control using cadexomer iodine,[165–167] and a significant difference was noted in the amount of pus compared with dextranomer.[165] Moreover, compared with dextrin polymer used as the base, cadexomer iodine was significantly superior in the bacterial disappearance rate and appearance rate of new bacteria in pressure ulcers.[167] Also, compared with a fibrinolysin-DNase mixture (containing chloramphenicol), no significant difference was noted, and cadexomer iodine is expected to show clinical efficacy similar to that of chloramphenicol.[166]
- Cadexomer iodine produces a bactericidal effect by slowly releasing iodine.[177] Dextrin polymer absorbs not only exudates but also bacteria.[177–179] Therefore, it is useful for the treatment of wounds rich in exudates and pus. However, old polymer beads must be completely washed off when the dressing is changed, so the material should not be used for pockets that are difficult to wash.[175] If exudates are deficient, it may dry the wound surface and delay wound healing. In the phase with well-developed granulation tissue, iodine may damage the granulation tissue. In addition, caution is needed with respect to iodine allergies.[175]
- There are three RCT concerning infection control using silver sulfadiazine, comparing it with povidone-iodine solution, a base, and gentamicin sulfate.[168–170] Silver sulfadiazine showed a significantly superior infection-controlling effect compared with povidone-iodine solution.[168] In a double-blind trial comparing it with the base, it showed a significantly stronger effect.[169] In a double-blind trial comparing it with gentamicin sulfate cream, no significant difference was noted in the efficacy rate.[170]
- Silver sulfadiazine produces an infection-controlling effect on the wound surface due to the antibacterial action of the silver it contains on cell membranes and cell walls,[180,181] and it suppresses the formation of biofilms by *S. aureus* including MRSA.[182] Because an emulsion base is used, necrotic tissue is softened and lysed, and this exerts a wound surface cleaning effect. Caution is necessary when silver sulfadiazine is used for wounds with abundant exudates, because it may cause edema at the wound surface.[175] The effectiveness of silver sulfadiazine is attenuated when used with povidone-iodine. Moreover, its use with other drugs, particularly, external enzyme preparations, should be avoided.[175]
- There are three non-blinded RCT concerning infection control using povidone-iodine,[171–173] and it was found to be significantly superior compared with sucrose and calf blood extract. In addition, it was superior to lysozyme chloride when compared in non-disinfected patients.
- Povidone-iodine sugar produces an infection-controlling effect due to the antibacterial action of the iodine it contains.[183] Sucrose inhibits the growth of bacteria and suppresses the formation of biofilms by *S. aureus* including MRSA.[184] It alleviates edema at the wound surface due to its water-absorbing effect, promotes collagen synthesis by fibroblasts, and thus induces satisfactory granulation.[185] However, in wounds deficient in exudates, it may dry the wound surface and delay healing.[175] In the red stage when granulation tissue is well-developed, povidone-iodine may damage granulation tissue. In addition, caution is needed with respect to iodine allergies.[175]
- There is one case report concerning infection control using povidone-iodine gel.[174] The skin lesions included pressure ulcers in two of the 20 patients. The treatment caused disappearance of *S. aureus* and *P. aeruginosa*, which did not disappear when treated with ointments containing antibiotics.
- Povidone-iodine gel produces an infection-controlling effect due to the antibacterial activity of iodine, and its bactericidal effect is stronger than that of povidone-iodine sugar.[183,186] It exerts a strong antiseptic (or inactivating) effect not only on bacteria including MRSA but also on viruses.[187,188] It may cause transient hypothyroidism if used in large doses.[175] Caution for iodine allergies is necessary.[175]
- There is only an expert opinion concerning the infection-controlling effect of iodoform.[175] It exerts an infection-controlling effect through the bactericidal action of iodine.
- Iodoform exerts a bactericidal effect through the iodine released when it is dissolved in bodily fluids. It exhibits odor control and secretion control effects and is mildly analgesic as well.[189] Large-scale use has caused symptoms of poisoning, and caution is needed with respect to iodine allergies.[175]
- There is only an expert opinion on infection control using iodine ointment,[176] and it is considered appropriate for infected wounds.
- Iodine ointment exhibits iodine-releasing properties similar to that of cadexomer iodine. Its bactericidal effect is also

similar to that of cadexomer iodine, with no observed growth of any of the bacterial species examined, including MRSA.[190,191] By forming a gel, it is expected to contribute to a decrease in stress during treatment.[176] Its water-absorbing capacity is 7.3 mL/g of purified water,[191] which ranks highest among various preparations. Therefore, it is appropriate for wounds rich in exudate, but in wounds deficient in exudate, it does not easily form a gel,[191] and caution is needed with respect to drying of the wound surface. Caution is needed with respect to iodine allergies.

- There are two RCT concerning ointments containing antibiotics.[160,170] A double-blind trial of gentamicin sulfate (cream-based) versus silver sulfadiazine[170] was performed, and no significant difference was noted between the two in the changes in bacteria count during a 2-week evaluation period. In a trial of a fibrinolysin-DNase mixture (containing chloramphenicol) versus cadexomer iodine,[166] the disappearance rate of *P. aeruginosa* after 4 weeks was higher for the former, but the appearance rates of new bacteria after 4 and 6 weeks did not differ significantly. Also, in a large-scale RCT of white petrolatum versus bacitracin-containing ointment for surgical wounds, there was no significant difference in the infection rate, but as contact dermatitis occurred in a small number of patients treated with bacitracin-containing ointment, white petrolatum was concluded to be safer.[192] None of these studies presented evidence indicating superiority of ointments containing antibiotics, and as discussed in one of the references,[170] ointments containing antibiotics tend to be used for a long period of time to control infection of deep pressure ulcers and so should be avoided due to the possibility of microbial substitution. For the same reason, the use of fradiomycin sulfate-crystalline trypsin cannot be recommended.

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CQ21: WHAT DRESSING MATERIALS SHOULD BE USED AS LOCAL TREATMENTS FOR CONTROLLING INFECTION?

Description of recommendation: For dressing material when wound infection is localized, we recommend the use of silver-containing Hydrofiber (1A), silver-containing polyurethane foam (1A) and silver-containing alginate (1A).

Recommendation level: 1A.

Silver-containing Hydrofiber, silver-containing polyurethane foam and silver-containing alginate.

Commentary:

- There is one systematic review using silver-containing Hydrofiber and silver-containing polyurethane foam for chronic wounds requiring infection control.[193] The evidence level is I and the recommendation level is 1A. Silver-containing dressing materials are reported to be useful for controlling infection, but pressure ulcers only make up a small proportion of chronic wounds. In addition, there are few quality RCT.
- There is one report summarizing three RCT using silver-containing alginate and silver-containing polyurethane foam for chronic wounds requiring infection control.[194] There are two RCT using silver-containing alginate primarily for chronic wounds with local signs of infection,[195,196] and differences in infection control can be seen among silver-containing dressing materials. The evidence level is II and the recommendation level is 1A.
- There is one systematic review using silver-containing Hydrofiber and silver-containing polyurethane foam for chronic wounds requiring infection control.[193] Four of 14 studies included investigate infection control, and a significantly superior infection control effect was seen compared with the control in each of these studies. A significant difference against the control was also seen in a number of variables such as wound improvement, infection control, moisture balance and epithelialization, but the number of pressure ulcer cases was 210 out of 1285 chronic wounds, which was a low number. In addition, there were few quality RCT, and so an effect from confounding factors cannot be ruled out from the conclusion of a significant difference in these variables.
- There is one report summarizing three RCT using silver-containing alginate and silver-containing polyurethane foam for chronic wounds requiring infection control.[194] During 4 weeks of management of the infected chronic wounds, there was no evidence supporting the use of these silver-containing dressings. However, RCT studied in this report[197,198] found that compared with a dressing not containing silver, the use of silver-containing polyurethane foam resulted in a superior reduction in wound area, reduction in necrotic tissue, and control of exudates, odor and level of pain when changing dressings.[197] In addition, the use of silver-containing alginate compared with alginate resulted in wound infection rates of 33% and 46%, respectively. Although this difference was not significant, the rate for the silver-containing alginate was lower. Furthermore, the rate of cure after 4 weeks was significantly more favorable with silver-containing alginate.[198] There are also two RCT on the use of silver-containing alginate primarily for chronic wounds with local signs of infection.[195,196] In these studies, pressure ulcers occurred in 24 of 42 patients,[195] and in 12 of 36 patients,[196] respectively, and the comparison was with alginate that did not contain silver. In the first study, no significant difference in the clinical score for infection was found after 2 weeks, but it was reported that the state of local infection had improved in the silver-containing group.[195] The other RCT showed a significant improvement in the clinical score for infection in the silver-containing group after 4 weeks, and the wound area was also reported to have been reduced significantly.[196]
- Hydrofiber can absorb approximately 30 times its own weight.[199] With approximately double the moisture retention capacity of alginate, Hydrofiber maintains a moist environment appropriate for healing for a prolonged period, and promotes granulation.[199] It prevents lateral spread of absorbed exudates, preventing maceration of healthy skin surrounding the wound.[199] In addition, silver-containing Hydrofiber seals exudates including bacteria by forming a gel on contact with the wound and locks exudate in the dressing, thus preventing backflow into the wound. By releasing silver ions in this state, bacteria in exudates can be rapidly and effectively sequestered.[200–202]
- Polyurethane foam can absorb approximately 10 times its own weight in exudates, and promotes granulation and epithelialization by maintaining an appropriate moist environment. It does not leave residues at the wound from dissolution or detachment of the dressing material. In addition, the wound-contacting surface is a non-adhesive polyurethane net, and so it is unlikely to rub off the newly formed epithelium even if it slides from the wound surface.[199] The silver-containing hydrophilic polyurethane foam preparation exhibits antimicrobial action due to the release of silver, and so it can be used in wounds with a high likelihood of infection with exudates.
- Alginate can absorb 10–20 times its own weight.[199] By absorbing large volumes of exudates, it forms a gel that promotes healing by maintaining the wound surface in a moist environment.[203] In addition, calcium ions in the alginate and sodium ions in the blood and bodily fluids are exchanged at the contact surface with the wound, and the calcium ions disperse within the capillaries due to the resulting concentration gradient. This has a hemostatic effect.[204] Silver-containing preparations have a wound-cleansing effect due to the silver ions released as the exudates are absorbed exerting a bactericidal effect against bacteria inside and at the wound

surface. Thus, they may be used for wounds with a high likelihood of infection.

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M: CORRECTION OF MOISTURE IMBALANCE, MANAGEMENT OF EXUDATE

CQ22: WHAT TOPICAL AGENTS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS DURING THE BLACK TO YELLOW STAGES WITH EXCESSIVE EXUDATES?

Description of recommendation: The use of cadexomer iodine (1A), dextranomer (1A), povidone-iodine sugar (1A), and iodine ointment (1D) is recommended in stages with excessive exudates.

Recommendation levels: 1A, 1D.

Cadexomer iodine, dextranomer, povidone-iodine sugar (1A).

Iodine ointment (1D).

Commentary:

- There are three RCT[205–207] concerning the control of exudates using cadexomer iodine and one RCT each for dextranomer[208] and povidone-iodine sugar.[209] Thus, the evidence level is II. Each of these RCT indicated superiority of these treatments compared with the control drug, and so the recommendation level is 1A.
- There are only expert opinions concerning the control of exudates using iodine ointment,[210,211] and so the evidence level is VI. It is an appropriate selection as a base for maintaining a moist environment when exudates are excessive and is widely used in the clinical setting, and so the recommendation level is 1D.
- Exudates are often abundant in pressure ulcers in the yellow stage, and their control is desirable from the standpoint of wound bed preparation. In addition, changing dressings frequently is disadvantageous in terms of labor and cost. However, the use of strongly absorbent material may cause drying of the wound surface and interfere with moist wound healing. Therefore, wounds must be carefully observed, keeping in mind the possibility of a decrease in exudate volume as the condition of the wound surface improves, and a change in treatment approach must be evaluated according to the algorithm if a drying trend is observed.
- There are three RCT concerning the control of exudates using cadexomer iodine.[205–207] Compared with dextranomer, the exudate volume significantly improved with cadexomer iodine.[205] Exudates also significantly reduced with cadexomer iodine compared with a fibrinolysin-DNase mixture.[206] Moreover, the exudate-absorbing effect of cadexomer iodine did not differ significantly in an RCT comparing the dextrin polymer base alone.[207] Therefore, this effect is derived from the dextrin polymer.
- Cadexomer iodine produces a bactericidal effect by slowly releasing iodine.[212] Dextrin polymer absorbs not only exudates but also bacteria.[212–214] Therefore, it is useful for the treatment of wounds rich in exudates and pus. However, old polymer beads must be washed off completely at dressing changes, and so it should not be used for undermining that are difficult to wash.[215] If exudates are scarce, the treatment may dry the wound surface and delay wound healing. In a stage with well-developed granulation tissue, this may be damaged by iodine. In addition, caution is required with respect to iodine allergies.[215]
- There is one non-blinded RCT concerning exudate control using dextranomer.[208] The exudate volume significantly improved when compared with the improvement rate using physiological saline dressing.
- Dextranomer is reported to clean the wound surface by absorbing exudates.[216] It absorbs not only exudates but also bacteria.[217] It is available as a powder and as a paste, prepared by the addition of macrogol and purified water, and both are used as specified materials covered by the National Health Insurance. Because they are water-absorbing preparations, they are favorably indicated for patients with excessive to appropriate exudates, although caution for drying of the wound surface is necessary.
- There is one non-blinded RCT concerning the control of exudates using povidone-iodine sugar.[209] Povidone-iodine sugar showed significantly higher improvement rates in both serous and pussy secretions compared with lysozyme chloride.

- The exudate-absorbing effect of povidone-iodine sugar did not differ significantly compared with sucrose, which is one of its primary components, alone,[218,219] so this effect is considered to be derived from white sugar. If exudates are deficient, the treatment has been reported to dry the wound surface and delay healing.[215] Similarly, in a phase with well-developed granulation tissue, granulation tissue may be damaged by povidone-iodine gel. In addition, caution is required with respect to iodine allergies.[215]
- There are only expert opinions on the control of exudates using iodine ointment.[210,211] By compounding a gelling agent such as partially neutralized polyacrylic acid with macrogol as the base, the preparation is designed to form a gel when it absorbs exudates.
- When in gel form, iodine ointment is expected to contribute to a reduction in stress during treatment.[220] Its water-absorbing capacity is 7.3 mL/g of purified water,[221] which ranks best among various preparations. Therefore, it is appropriate for wounds rich in exudates but the preparation does not gel easily in wounds deficient in exudates, and caution against drying of the wound surface is necessary.[210] Caution is also needed with respect to iodine allergies.

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CQ23: WHATDRESSING MATERIALS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS DURING THE BLACK TO YELLOW STAGES WITH EXCESSIVE EXUDATES?

Description of recommendation: When there are excessive exudates, highly absorbent alginate (1A), polyurethane foam (including silver-containing preparations) (1A), chitin, Hydrofiber (including silver-containing preparations) (1C), Hydropolymer (1C) and polyurethane foam/soft silicone (1D) are recommended.

Recommendation levels: 1A, 1C, 1D.

Alginate, polyurethane foam (including silver-containing preparations) (1A).

Chitin, Hydrofiber (including silver-containing preparations), hydropolymer (1C).

Polyurethane foam/soft silicone (1D).

Commentary:

- There are two RCT using alginate for local treatment of deep pressure ulcers.[222,223] The evidence level is II and the recommendation level is 1A. Alginate was shown to have a significantly superior cure rate compared with dextranomer[222] and hydrocolloids.[223]
- There is one meta-analysis investigating the exudate absorption by silver-containing dressing materials including silver-containing polyurethane foam.[224] The evidence level is I and the recommendation level is 1A. There were few cases of pressure ulcers among the chronic wounds studied, and polyurethane foam was considered in four out of the eight studies analyzed. Nonetheless, its ability to absorb exudates was found to be significantly superior to the control.
- One RCT compared the exudate absorption ability of polyurethane foam with that of hydrocolloids.[225] The evidence level is II and the recommendation level is 1A. Polyurethane foam was significantly superior. There are case reports concerning the exudate absorption abilities of chitin,[226,227] Hydrofiber[228,229] and hydropolymer.[230] The evidence level is V and the recommendation level is 1C.

- There are no studies investigating the exudate absorption properties of polyurethane foam/soft silicone for pressure ulcers in the black through yellow stages. There are only expert opinions, resulting in an evidence level of VI, but because it is expected to be equivalent to that of polyurethane foam, the recommendation level was set at 1D. There is one RCT studying its use for grade II (EPUAP) pressure ulcers compared with hydropolymers,[231] but no significant difference was found between the two groups in exudate absorption.
- There are two RCT using alginate for deep pressure ulcers requiring exudate control.[222,223] The cure rate was significantly higher than with dextranomer.[222] In addition, when pressure ulcers were treated with alginate for the first 4 weeks and with hydrocolloids for the subsequent 4 weeks, with the control group treated with hydrocolloids alone for 8 weeks, the ulcer size reduction rate was significantly superior than in the control group.[223]
- Alginate can absorb 10–20 times its weight of liquid.[232] It forms a gel by absorbing a large volume of exudates, and promotes healing by maintaining a moist environment on the wound surface.[233] In addition, calcium ions in the alginate and sodium ions in the blood and bodily fluids are exchanged at the contact surface with the wound, and the calcium ions disperse within the capillaries due to the resulting concentration gradient. This has a hemostatic effect.[234] Silver-containing preparations have a wound-cleansing effect due to the silver ions released as the exudates are absorbed and exert a bactericidal effect against bacteria inside and at the wound surface. Thus, they may be used for wounds with a high likelihood of infection.
- There is one meta-analysis investigating the exudate absorption by silver-containing dressing materials including silver-containing polyurethane foam when used at chronic wounds.[224] There were only 200 (16.83%) cases of pressure ulcers, which was a low number, and silver-containing polyurethane foam was considered in only four of the eight studies analyzed. In all four of these studies, the ability of silver-containing polyurethane foam to absorb exudates was found to be significantly superior to the control. However, none of these were limited only to pressure ulcers with excessive exudates in the black to yellow stages.
- There is one RCT evaluating the exudate-absorbing ability of polyurethane foam.[225] It was significantly superior to hydrocolloids in absorption ability and ease of detachment, but no significant difference was noted in the dressing period. However, the subjects were not limited only to pressure ulcers with excessive exudates in the black to yellow stages.
- Polyurethane foam absorbs approximately 10 times its weight in exudates, and promotes granulation and epithelization by maintaining an appropriate moist environment. It leaves no residue at the wound due to dissolution or detachment of the dressing material. In addition, its wound-contacting surface is made of a non-adhesive polyurethane net, and so it is unlikely to rub off the newly formed epithelium even if it slides from the wound surface.[232] The silver contained in the hydrophilic polyurethane foam as a silver-containing preparation exhibits an antibacterial effect, and so it can be used in wounds with a high likelihood of infection with exudates.
- Polyurethane foam/soft silicone uses a self-adherent adhesive made from soft silicone at the wound-contacting surface of polyurethane foam. The soft silicone is highly accommodating of the texture of the skin[235] and so is considered to induce the lowest level of pain and skin damage during dressing changes. It is possible to peel away a portion of the dressing layer to observe the wound, and if it is judged too early to change the dressing, it can be returned to its previous state.
- There are two case reports concerning the exudate-absorbing ability of chitin.[226,227] However, it has been reported both to have[226] and not to have[227] an exudate-controlling effect. In addition, neither of these were limited only to pressure ulcers with excessive exudates in the black to yellow stages.
- Because chitin cotton is flexible, it can be readily applied to the wound surface for its protection.[226] It can absorb 25 times its weight in liquid.[227] It also promotes granulation, and granulation tissue that develops underneath is reddish and of high quality.[226] Because it is capable of astriction, it is useful for hemostasis after debridement.[227]
- There are two case reports on the exudate-absorbing ability of Hydrofiber,[228,229] reporting an improvement in exudates. However, neither of these were limited only to pressure ulcers with excessive exudates in the black to yellow stages.
- Hydrofiber can absorb approximately 30 times its weight in liquid.[232] It has approximately double the water-retaining capacity of alginate, maintains a moist environment optimal for curing over a prolonged period of time and promotes granulation.[232] It prevents the lateral spread of exudates that it has absorbed, thus preventing maceration of the healthy skin around the wound.[232] In addition, Hydrofiber seals exudates including bacteria by forming a gel on contact with wound fluid and locks exudate in the dressing, thus preventing their reflux back to the wound. Because silver ions are released in this state, bacteria in the exudates can be rapidly and efficiently sequestered.[236–238]
- There is one case report on the use of hydropolymer for pressure ulcers requiring the control of exudate,[230] and satisfactory absorption of exudates was reported. However, this report was not limited only to pressure ulcers with excessive exudates in the black to yellow stages.
- Hydropolymer absorbs exudates, and its exudate processing ability is enhanced by active evaporation of the absorbed exudate.[230] The adhesive is a water-based polyurethane gel, and thus, this dressing material causes little irritation of the skin.[230] It swells by absorbing exudates and fits into the depression of the ulcer.[232] The swollen polymer does not leave debris in dressing change.[239]

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CQ24: WHAT TOPICAL AGENTS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS DURING THE BLACK TO YELLOW STAGES WHEN EXUDATE LEVELS ARE LOW?

Description of recommendation: The use of silver sulfadiazine (1D), oil-based ointments (1D), such as white petrolatum, zinc oxide and dimethyl isopropyl azulene, is recommended when exudate levels are low.

Recommendation level: 1D.

Silver sulfadiazine, oil-based ointments such as white petrolatum, zinc oxide and dimethyl isopropyl azulene.

Commentary:

- The only reports on topical agents to be used in the yellow stage when exudates are deficient are expert opinions,[240–242] and so the evidence level is VI. However, because silver sulfadiazine is widely used with the objective of removing necrotic tissue at the same time as controlling infection, its recommendation level was set at 1D. In addition, oil-based ointments, such as white petrolatum, zinc oxide and dimethyl isopropyl azulene, have a wound surface protective effect, and so the recommendation level was set at 1D.
- In deep pressure ulcers, drying of the wound surface leads to delay in healing.[240] To maintain the wound in an appropriate moist environment, it is necessary to use a drug with an appropriate water content or an oil-based ointment with a wound surface protection effect. Particularly, in the yellow stage, a preparation with both debriding and infection-controlling effects as well as a water-retaining effect is ideal.
- Because silver sulfadiazine preparations are emulsion-based, they produce a wound surface cleaning effect through the softening/autolysis of necrotic tissue by providing moisture to the wound. In a stage during which the margins of black necrotic tissue are raised, these preparations are considered to facilitate surgical debridement, and control infection of the wound surface silver against bacterial cell membranes and cell walls.[241] Caution is necessary when the exudate levels are high as there is risk of edema at the wound surface.[242] In addition, their efficacy is attenuated when used with povidone-iodine. Their concomitant use with other drugs, particularly external enzyme preparations, should be avoided.[242]
- Oil-based ointments typified by highly water-repellent white petrolatum, such as zinc oxide and dimethyl isopropyl azulene ointments, are useful when exudate levels are low, because they protect the drying wound surface.[242] However, they have no infection-controlling or debriding effect on the wound surface.
- The aimless use of ointments containing antibiotics for deep pressure ulcers in the chronic phase should be avoided as a rule due to the possibility of resistant strains appearing (see CQ20).

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CQ25: WHAT DRESSING MATERIALS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS DURING THE BLACK TO YELLOW STAGES WHEN EXUDATE LEVELS ARE LOW?

Description of recommendation: The use of hydrogels (1B) is recommended when dried necrotic tissue has adhered to the wound and exudate levels are low.

Recommendation level: 1B.

Commentary:

- There is one RCT concerning the debriding effect of hydrogels in pressure ulcer patients with necrotic tissue.[243] The evidence level is II and the recommendation level is 1B. Although the wound size reduction rate was significantly higher with hydrogels compared with dextranomer, the necrotic tissue removal rate showed no significant difference between the two materials.
- Hydrogels not only absorb and retain exudates, but also macerate the wound and necrotic tissue because of the water they contain, promoting their elimination.[244] In addition, hydrogel causes no pain, redness or inflammation of the surrounding healthy skin unlike chemical debridement using enzyme preparations.[245] If necrotic tissue is found to be macerated at dressing change, surgical debridement should be also performed to the extent possible.[245]

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E: TREATMENT OF NON-ADVANCING OR UNDERMINED EPIDERMAL MARGIN, MANAGEMENT OF THE WOUND EDGE

CQ26: WHAT LOCAL TREATMENTS SHOULD BE PERFORMED FOR UNDERMINED PRESSURE ULCERS?

Description of recommendation: For wound surfaces with high exudate levels in an undermining, the use of povidone-iodine sugar (1B) is recommended. If exudate levels are low, the use of trafermin (1C) or tretinoin tocoferil (1D) is recommended.

However, if no improvement is observed with these treatments, surgical treatments or physical therapy should be evaluated.

Recommendation levels: 1B, 1C, 1D.

Povidone-iodine sugar (1B).

Trafermin (1C).

Tretinoin tocoferil (1D).

Commentary:

- There is one non-randomized comparison study of povidone-iodine sugar relative to undermining.[246] The evidence level is III and the recommendation level is 1B.
- There is one non-randomized comparison study of trafermin relative to undermining.[247] The evidence level is III, but no significant difference was found in comparison with various granulation-promoting topical agents, so the recommendation level is 1C.
- There are no studies concerning treatment of pockets with tretinoin tocopherol other than an expert opinion,[248] and so the evidence level is VI. If exudate levels are low, it is an appropriate choice as a base for maintaining a moist environment and as it is widely used in the clinical setting; therefore, the recommendation level was set at 1D.
- Because necrotic tissue is likely to persist in deep parts of an undermining, this prevents generation of new granulation tissue and makes infection control difficult as well. Moreover, drainage of exudates tends to become insufficient, causing an excessively moist condition. In addition, undermining is prone to shearing due to body movements, making them likely to be enlarged further. Therefore, these problems should be identified in order to provide appropriate care to individual patients and to strive to eliminate compression and shearing as causes of undermining. However, if the undermining does not disappear even after elimination of its causes by sufficient care, treatment with topical agents should not be continued aimlessly and surgical treatments or physical agents such as NPWT should be considered.
- There is one non-randomized uncontrolled comparative trial concerning povidone-iodine sugar,[246] reporting improvements for undermining. In 36 patients with skin ulcers complicated by diabetes (including six with pressure ulcers), at least an improvement was observed in eight (88.9%) of the nine patients with undermining formation of ulcers.
- Advantages of povidone-iodine sugar include an excellent infection-controlling effect as well as promotion of favorable granulation due to absorption of exudates and suppression of edema.[248] However, if exudate levels are low, it may dry the wound surface and delay healing.[248] In a stage with well-developed granulation tissue, povidone-iodine may damage granulation tissue. In addition, caution is needed with respect to iodine allergies.[248]
- There is one non-randomized comparative trial concerning the effectiveness of trafermin for the treatment of undermining.[247] Comparison of various topical agents exerting granulation-promoting effects showed that trafermin accelerated the cure of pockets but not significantly. There are also case reports that size of undermining was reduced by the use of trafermin.[249,250] While there are case reports of inserting chitin sprayed with trafermin into undermining to transport the drug to the deepest portions of the pockets[251] and of the concomitant use of trafermin with NPWT,[252] the evaluation is difficult as trafermin was not used alone.
- Because trafermin has strong angiogenic and granulation-promoting activity,[253–255] it is expected to be effective for closing pockets. It may be used in combination with other topical agents and dressing materials to fill dead spaces and retain moisture.[248]
- Tretinoin tocopherol promotes granulation and angiogenesis due to its effects on promoting fibroblast migration, cell migration and cell proliferation.[256–259] Because an emulsion base having a water content of 70% is used, the drug is appropriate for wounds showing a drying tendency,[248] but not for wounds with high exudate levels or showing marked edema.

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CQ27: HOW ARE UNDERMINED "POCKET" PRESSURE ULCERS SURGICALLY CUT OPEN?

Description of recommendation: Surgical opening of undermined pressure ulcer, with appropriate bleeding control, is recommended. Whether to remove the overlying skin entirely should be determined on the individual patient's conditions.

Recommendation level: 1C.

Commentary:

- There is one prospective cohort study on surgical opening of undermined pressure ulcers;[260] the evidence level is IVa. Also, there are four case studies of the surgical opening;[261–264] the evidence level is V. The recommendation level is 1C.
- In a prospective cohort study,[260] surgical opening was performed in 39 out of 162 undermined pressure ulcers, and the evaluation was made 4 weeks after the surgery. The surgical opening significantly reduced the DESIGN-R values.
- When the inside of the undermined pressure ulcers is infected, and it affects the patient's general condition, surgical opening of the undermined ulcer must be performed (also see CQ16). The opening with electrosurgery devices will minimize the bleeding. The patient's general condition and his medications, such as antiplatelets and anticoagulants, must be evaluated before the procedure. Guidelines for cardiovascular diseases recommended minor surgeries in which hemorrhage can be controlled easily to be performed without discontinuing these drugs.[265] Guidelines for cerebrovascular diseases recommended that oral warfarin should be continued and that antiplatelet therapy can be continued.[266] The risk of hemorrhage should be evaluated in individual patients with attending physicians.
- Whether to remove the overlying skin partially or entirely will be determined on the subsequent treatments and care. The following factors will be considered:

1. Infection in the undermined lesion, necrotic tissue that cannot be completely removed through the small opening, "pocket in pocket" formation. These are indications for the entire removal of the overlying skin.
2. Prospect of the subsequent treatment. Plastic surgery: skin graft or flap, NPWT or conservative therapy with ointments and dressing materials. Unless NPWT will not be performed, remaining overlying skin often interferes with epithelization.
3. Who will treat the pressure ulcer after the surgical procedure? Physicians? Hospital nurses? Home care nurses? Patien's family members? It is not advisable to leave the overlying skin unremoved, if the nurses or the family members are not expertized in wound treatment.

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CQ28: IS NEGATIVE-PRESSURE WOUND THERAPY USEFUL FOR UNDERMINED "POCKET" PRESSURE ULCERS?

Description of recommendation: NPWT can be performed using either commercially available systems or handmade instruments. Both are recommended.

Recommendation level: 1C.

Commentary:

- There are five case reports on the efficacy of NPWT for undermined pressure ulcers.[267–271] The evidence level is V and the recommendation level is 1C.
- V.A.C.® Therapy has been marketed in Japan since year 2010, followed by RENASYS Negative-Pressure Wound Therapy, SNAP Therapy System and PICO system for NPWT. Currently, these four systems are approved by the Japanese National Health Insurance Program. Until 2010, NPWT had been performed with handmade instruments prepared by a combination of occlusive dressing materials and aspiration devices. Both commercially available systems and handmade instruments were effective, according to the case reports.
- Health insurance payment can be claimed only on the use of the commercially available devices. The same amount of payments is claimable regardless of the products. The claimable period is up to 3 weeks. With written comments on a claim, another 1 week payment can be claimed. For NPWT on outpatients, the SNAP Therapy System and PICO system for NPWT can be claimed. The claimable period is the same as that of inpatients. In order to claim the payment, visiting an outpatient clinic is mandatory. It is not available for patients only receiving home care.
- Either with commercially available systems or with handmade instruments, removal of necrotic tissues and control of infection are among the basic principles of wound treatment. We often encounter the worsening of infection during NPWT.[272–274] NPWT is not indicated for the ulcer with infectious foci. In order to perform NPWT safely and effectively, careful observation, appropriate debridement and improvement in the patient's general condition are advisable.

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Red and White stages: Moist Wound Healing (CQ29–31)

CQ29: WHAT TOPICAL AGENTS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS IN THE RED TO WHITE STAGES?

Description of recommendation: The use of trafermin (1A), tretinoin tocoferil (1A), prostaglandin E1 (1A), lysozyme chloride (1B) and oil-based ointments (1D) such as calf blood extract, white petrolatum, zinc oxide and dimethyl isopropyl azulene is recommended for wounds with appropriate to deficient exudates.

The use of bucladesine sodium (1A), aluminum chlorohydroxy allantoinate (Alcloxa) (1B) and povidone-iodine sugar (1B) is recommended for wounds with excessive exudates or marked edema (B).

Recommendation levels: 1A, 1B, 1D.

Wound surfaces with appropriate to deficient exudates:
Trafermin, tretinoin tocoferil, prostaglandin E1 (1A).
Lysozyme chloride (1B).
Oil-based ointments such as calf blood extract, white petrolatum, zinc oxide and dimethyl isopropyl azulene (1D).

Wound surfaces with excessive exudates or marked edema:
Bucladesine sodium (1A).
Aluminum chlorohydroxy allantoinate (Alcloxa), povidone-iodine sugar (1B).

Commentary:

- There are two RCT for each trafermin,[275,276] tretinoin tocopherol[277,278] and bucladesine sodium,[279,280] and one RCT concerning the granulation-promoting and wound size-reducing effects of prostaglandin E.[281] The evidence level is II and the recommendation level is 1A. Trafermin resulted in a significantly higher rate of wound size reduction compared with granulocyte macrophage colony-stimulating factor (GM-CSF). Tretinoin tocopherol was found to be superior to both lysozyme chloride and bendazac-containing ointment.

Bucladesine sodium was found to be significantly superior in reducing the size of ulcers compared with its base of macrogol. Prostaglandin E was found to be significantly superior in reducing the depth and area of pressure ulcers compared with lysozyme chloride.

- There are three non-blinded RCT on granulation and ulcer size when using lysozyme chloride.[282–284] The evidence level is II but the recommendation level was set at 1B because of defects in study design.
- The use of calf blood extract and oil-based ointments including white petrolatum, zinc oxide and dimethyl isopropyl azulene was recommended solely on expert opinion;[285] thus, the evidence level is VI. It would be appropriate to use an oil-based ointment with the objective of moist wound healing, and in addition, because such ointments are widely used in the clinical setting, the recommendation level was set at 1D.
- There are two RCT regarding aluminum chlorohydroxy allantoinate,[286,287] and so the evidence level is II. It promoted granulation significantly compared with the base or calf blood extract. However, as it is an old drug, and the frequency of its use has decreased with the development and sale of new drugs, the recommendation level was set at 1B.
- There are four non-blinded RCT on granulation and ulcer size when relative to povidone-iodine sugar,[276,288–290] and so the evidence level is II. Two of the non-blinded RCT using lysozyme chloride as a control found that povidone-iodine sugar was significantly superior in promoting granulation, but the recommendation level was set at 1B because of defects in study design.
- In the latter half of treatment, the wound enters the red stage, and the risk of infection decreases. In this period, it is most important to maintain an appropriate moist environment. As favorable granulation tissue is formed, the wound begins to shrink. Therefore, the point of treatment is to select topical agents that protect the wound surface, promote granulation and reduce the wound size. In Japan, multiple topical agents with a granulation-promoting effect have been developed, and they should be selected according to the volume of exudates and the presence of edema at the wound surface. To implement a study design incorporating the concept of moist wound healing, it is necessary to focus on patients with pressure ulcers in the red stage in the latter half of treatment, but there are few such studies.
- There is one RCT comparing the wound size-reducing effect of trafermin with that of GM-CSF,[275] and the wound size reduction rate was reported to be significantly higher with trafermin. There is also an RCT using povidone-iodine sugar as a control,[276] and the ulcer depth reduction rate was reported to be significantly greater with trafermin. However, the use of povidone-iodine sugar as a control drug in the red period is considered questionable.
- Trafermin promotes wound healing due to its angiogenic and granulation-promoting effects.[291–293] While its wound healing effect is strong, it is difficult to maintain a moist environment at the wound using only a spray type preparation of this drug, and so the concomitant use of other topical agents or dressing materials is recommended.[285] Also, while trafermin is expensive, there is a case–control study concerning the cost-effectiveness of a dressing material alone versus trafermin plus a dressing material used until cure.[294] Although there was no difference in the cost of materials, the period until cure was markedly shortened with trafermin plus a dressing material, so the treatment was concluded to be economically advantageous considering the charges for treatments and hospitalization.
- There are two non-blinded RCT comparing tretinoin tocopherol with lysozyme chloride or bendazac-containing ointment.[278,279] Significant differences were observed in the granulation and ulcer size reduction rate compared with lysozyme chloride. Compared with the bendazac-containing ointment, there was no significant difference in the ulcer size reduction rate, but a significant difference was noted in granulation.
- Tretinoin tocopherol promotes granulation and angiogenesis by stimulating fibroblast migration, cell migration and cell proliferation.[295–298] Because an emulsion base with a water content of 70% is used, the preparation is appropriate for wounds showing a marked tendency toward dryness,[285] but not for exudate-rich or markedly edematous wounds.
- There is one non-blinded RCT comparing bucladesine sodium with lysozyme chloride.[280] While it was superior in improving ulcer size and granulation in intractable ulcers in general, there was no comparison made for pressure ulcers alone, and thus it is impossible to evaluate whether there was a significant difference. However, there is one double-blind RCT comparing it with a macrogol base,[281] and a significant decrease in the ulcer size was noted. There are also three non-randomized comparison studies with no adequate control group[299–301] indicating the promotion of granulation in pressure ulcers.
- Bucladesine sodium promotes wound healing by improving local blood flow and promoting angiogenesis, granulation and epidermis formation.[302–305] Because the base macrogol is absorbent, the preparation should be used for wounds with excessive exudates or marked edema. However, caution in drying of the wound is necessary during use in wounds with low exudate volume.
- Concerning prostaglandin E1, there is one non-blinded RCT comparing it with lysozyme chloride[277] which reported significant decreases in the area and depth of pressure ulcers.
- Prostaglandin E1 promotes wound healing due to its effects on increasing cutaneous blood flow[306] and promoting angiogenesis.[307,308] It also acts on fibroblasts to promote their proliferation[307,308] and stimulates keratinocyte proliferation by increasing the release of interleukin-6 from fibroblasts.[309,310] Because oleaginous plastibase is used as the base, the drug is appropriate for wounds with appropriate/deficient exudate, but not for exudate-rich or markedly edematous wounds.
- There are three non-blinded RCT concerning lysozyme chloride, evaluating its effects on granulation and ulcer size.[282–284] Improvements were observed by treatment with

lysozyme chloride, but no statistical analysis was performed in any of them. Furthermore, in all of these trials, the control drug was povidone-iodine sugar, which is considered questionable as a control drug in the red stage as this topical agent promotes drying.

- Lysozyme chloride has effects of promoting epidermal cell and fibroblast proliferation and promotes wound healing by stimulating mucopolysaccharide synthesis.[311–314] Because an emulsion base with a water content of 23% is used, its primary effect on the wound is protection rather than supply of moisture.
- Calf blood extract reportedly accelerates wound healing by activating tissue functions and promoting fibroblast proliferation, and thus promoting granulation and vascular regeneration.[315–317] Because an emulsion base with a water content of 25% is used, the preparation is appropriate due to its protective effect on wounds in which exudate levels are appropriate to low, but not for exudate-rich or markedly edematous wounds.
- Oil-based ointments typified by highly water-repellent white petrolatum, such as those containing zinc oxide and dimethyl isopropyl azulene, have wound-protecting effects and promote shrinking of the wound by maintaining a moist environment.[285] Therefore, they are appropriate for wounds with appropriate to low exudate levels, but not for exudate-rich or markedly edematous wounds. Although ointments containing antibiotics such as gentamicin are also oil-based, they are usually not used, as there is no need for infection control in the red stage and because the potential of development of resistant strains through long-term use (see CQ20).
- Povidone-iodine sugar is a drug that has the antibacterial effects of iodine in addition to the granulation promotion effects and exudate absorption effects of sucrose. It is often used for pressure ulcers in the yellow phase to control infection and due to the high level of exudates. If exudate levels are low, it can dry the wound surface, delaying wound healing.[318] In addition, during the phase with well-developed granulation tissue, povidone-iodine may damage the granulation tissue.[318] Thus, if it is to be used for granulation in the red phase, it is favorably indicated at the beginning of the red phase when exudate volume is high, or in the case of critical colonization. In addition, caution is needed with respect to iodine allergies.[318]
- Aluminum chlorohydroxy allantoinate promotes angiogenesis, drying of the wound surface, granulation, epidermal regeneration and reduction of the wound size.[319] There are powder and gel preparations used as its base, but as both are absorbent, they should be used for wounds with excessive exudate or marked edema and not for dry wounds.

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CQ30: WHAT DRESSING MATERIALS SHOULD BE USED FOR LOCAL TREATMENT OF PRESSURE ULCERS IN THE RED TO WHITE STAGES?

Description of recommendation: The use of hydrocolloids (1A), hydrogels (1B), hydropolymer (1B), polyurethane foam (1B) and polyurethane foam/soft silicone (1B) is recommended for wound surfaces with appropriate to deficient exudates.

The use of alginate (1C) or chitin (1C) is recommended for wound surfaces with excessive exudates or marked edema.

Recommendation levels: 1A, 1B, 1C.

Wound surfaces with appropriate to deficient exudates:
Hydrocolloids (1A).
Hydrogels, hydropolymer, polyurethane foam, polyurethane foam/soft silicone (1B).

Wound surfaces with excessive exudates or marked edema:
Alginate, chitin (1C).

Commentary:

- There is one systematic review[320] and one meta-analysis[321] on the use of hydrocolloids for the local treatment of pressure ulcers. The evidence level is I and the recommendation level is 1A. A significant difference in cure rate was found compared with saline gauze dressing,[320,321] but there was no significant difference compared with alginate, hydrogels or polyurethane foam.[320] In addition, none of these studies examined only pressure ulcers in the red to white stages.

- There are three RCT on the use of hydrogels for the local treatment of pressure ulcers,[322–324] and so the evidence level is II. Because no significant difference in cure rate was found compared with saline gauze dressing,[322,323] hydrocolloids[323] or povidone-iodine gauze,[324] the recommendation level was set at 1B.
- There are two RCT using hydropolymer for the local treatment of pressure ulcers,[325,326] and so the evidence level is II. Because no significant difference was noted in the cure rate in comparison with hydrocolloids, the recommendation level was set at 1B.
- There are three RCT using polyurethane foam for the local treatment of pressure ulcers,[327–329] and the evidence level is II. Because no significant difference was noted in the cure rate compared with saline gauze dressing,[327] hydrocolloids[328] and hydrogels,[329] the recommendation level was set at 1B.
- There is one RCT evaluating the use of polyurethane foam/-soft silicone for the local treatment of pressure ulcers.[330] The evidence level is II, but no significant difference was noted in the cure rate in comparison with hydropolymer, and so the recommendation level was set at 1B.
- There is one case report each on using alginate and chitin for the local treatment of pressure ulcers.[331,332] The evidence level is V and the recommendation level is 1C.
- The basis of moist wound healing is an appropriate water balance at the wound. Wound healing is delayed not only by drying due to extremely low exudate volume, but also due to excessive exudate volume. Because dressing materials to be used in the black-yellow stages with excessive (CQ23) and deficient (CQ25) exudate levels were mentioned above, pressure ulcers in the red-white stages with appropriate exudate levels are discussed in this section.
- In a systematic review of hydrocolloids for the local treatment of pressure ulcers,[320] the pressure ulcers were primarily at EPUAP grades II and III and the number of wounds cured, wound size reduction rate, period elapsed before requiring dressing change, exudate-absorbing capacity, pain on dressing change, adverse effects and cost was significantly more favorable compared with saline gauze dressing. The review concluded that hydrocolloids are superior in efficacy and cost to saline gauze dressing. However, compared with alginate, hydrogels and polyurethane foam, hydrocolloids are considered inferior in the number of wounds cured, wound healing time, wound size reduction rate, ease of handing, period elapsed before requiring dressing change, exudate-absorbing capacity and pain on dressing change. In particular, hydrocolloids were significantly inferior to alginate in wound size reduction rate and pain on dressing change, and were significantly inferior to polyurethane foam in period requiring dressing change, exudate-absorbing capacity and pain on dressing change. In terms of cost, hydrocolloids are reportedly more expensive than hydrogel and polyurethane foam. However, the difference in efficacy compared with alginate, hydrogel and polyurethane foam is slight, and a large-scale clinical trial is necessary. In addition, in the meta-analysis of hydrocolloids used for local treatment of pressure ulcers,[321] these were described as significantly promoting wound healing compared with conventional gauze dressings. However, pressure ulcers were considered in five of the 12 included studies, and only three of those found a significant difference. In addition, the target wounds were not restricted to pressure ulcers in the red-white stages in any of these trials.
- There is one RCT using clear and absorbent acrylic dressing material (Tegaderm Absorbent Clear Acrylic Dressing [TAAD]) and hydrocolloids (DuoDERM® CGF) for local treatment of pressure ulcers in the red-white stages.[333] When comparing comfort level, duration of application and wound healing, no significant difference was observed in wound healing, but TAAD was significantly superior in comfortableness. The mean duration of application was 5.7 days for TAAD and 4.7 days for hydrocolloids, and the difference was ascribed to the avoidance of unnecessary dressing changes because of the transparency of the material. In Japan, DuoActive ET is sold as a translucent hydrocolloid preparation allowing observation of the wound after the application.
- Hydrocolloids maintain a moist environment without adhering to the wound and prevent crust formation due to drying of the wound. By maintaining a moist environment at the wound, it promotes migration of epidermal cells and accelerates healing.[334] Hydrocolloids also occlude the wound and prevent exposure of denuded nerve endings to air, thus mitigating the characteristic tingling of shallow wounds.[335] As for silver-containing preparations, silver sulfadiazine contained in an adhesive layer has an antibacterial effect, and so can be used when there is a high likelihood of infection being caused in a wound with a low volume of exudates.
- There are three RCT using hydrogels for local treatment of pressure ulcers.[332–324] No significant difference was observed in the cure rate compared with saline gauze dressing[322,323] or hydrocolloids.[323] Hydrogels are considered to enable viewing of the wound after application, which can lead to acceptance for use.[323] Compared with povidone-iodine gauze,[324] no significant difference was noted in the wound size reduction rate, but as epithelization was noted significantly more frequently in the hydrogel (84%) than povidone-iodine gauze (54%) group, hydrogels are considered to promote healing by accelerating epithelization. However, the target wounds were not restricted to pressure ulcers in the red to white stages in any of these trials.
- Hydrogels not only promote granulation and epithelialization by maintaining a moist environment, but also control inflammation and mitigate pain due to their rapid cooling effect.[336] They also allow observation of the wound surface due to their transparency.[337]
- There are two RCT using hydropolymer for local treatment of pressure ulcers.[325,326] Although no significant difference was noted in the cure rate compared with hydrocolloids, hydropolymer was significantly superior in terms of cost,[324] leakage of exudates[326] and mitigation of odor.[326] However, the target wounds were not restricted to pressure ulcers in the red-white stages in either of these trials.
- Hydropolymer enhances the exudate processing ability by not only absorbing exudate but also actively evaporating the

absorbed exudate.[338] Hydropolymer using water-based polyurethane gel as the adhesive is a dressing material causing minimal irritation to the skin.[338] It also absorbs exudates and fits into the depression of ulcers.[336] Because it does not form a gel, it leaves no residue.[339]

- There are three RCT regarding the use of polyurethane foam for local treatment of pressure ulcers.[327–329] No significant difference was observed in the cure rate compared with saline gauze dressing,[327] but it resulted in significant reductions in the number of dressing changes and dressing cost, and so had superior cost performance. Compared with hydrocolloids,[328] no significant difference was noted in the cure rate, but polyurethane foam was significantly superior in ease of detachment and leakage. Compared with hydrogels,[329] there was no significant difference in cure rate or healing time. However, the target wounds were not restricted to pressure ulcers in the red-white stages in the comparison with hydrocolloids and hydrogels.
- Polyurethane foam can absorb approximately 10 times its weight in exudates, and promotes granulation and epithelization by maintaining an appropriate moist environment. It leaves no residues at the wound due to dissolution or detachment of the dressing material. It is also unlikely to cause detachment of the newly formed epithelium even if it is displaced from the wound surface, because the surface that comes into contact with the wound is made of a non-adhesive polyurethane net.[336] As for silver-containing preparations, the silver contained in hydrophilic polyurethane foam exerts a bactericidal effect, and so it can be used when there is a high likelihood of infection alongside exudates.
- There is one RCT on the use of polyurethane foam/soft silicone on EPUAP grade II pressure ulcers.[330] There was no significant difference in cure rate comparison with hydropolymer, but it had significantly lower loss/maceration/residue of skin surrounding the wound.
- Polyurethane foam/soft silicone uses a self-adhesive agent made from soft silicone at the wound-contacting surface of the polyurethane foam. Soft silicone is highly accommodating of skin texture[340] and so is considered to induce the lowest levels of pain and skin damage during dressing changes. It is possible to peel away a portion of the dressing layer to observe the wound, and if it is judged too early to change the dressing, it can be re-positioned to its previous state.
- There is one case report of the use of alginate for local treatment of pressure ulcers.[331] It was used for 50 patients with International Association for Enterostomal Therapy grade II pressure ulcers and 50 patients with grade III pressure ulcers and showed a wound size-reducing effect. All grade II pressure ulcers were cured with a mean treatment period of 17.9 days. Grade III pressure ulcers were cured in 32 patients (64%) with a mean treatment period of 55.7 days.
- Alginate can absorb 10–20 times its weight of liquid.[336] It promotes healing by absorbing a large volume of exudates, gelling and thus maintaining a moist environment over the wound surface.[337] In addition, calcium ions in the alginate and sodium ions in the blood and bodily fluids are exchanged at the contact surface with the wound, and the calcium ions disperse within the capillaries due to the resulting concentration gradient. This has a hemostatic effect.[341] Silver-containing preparations have a wound-cleansing effect due to the silver ions released as exudates are absorbed exerting a bactericidal effect against bacteria inside and at the wound surface. Thus, they may be used for wounds with a high likelihood of infection.
- There is one case report on the use of chitin for local treatment of pressure ulcers.[332] It was used in 32 patients with pressure ulcers (to the papillary layer of the dermis in 11 patients and deeper than that in 21) and was found to be effective for controlling exudates, protecting granulation tissue, promoting granulation and inducing epidermal formation.
- Chitin cotton is flexible and easy to apply to the wound surface for protection purposes.[332] It absorbs 25 times its weight of liquid.[342] It also promotes granulation and induces the formation of reddish, high-quality granulation tissue.[332] It can be used for pressure dressing and is useful for hemostasis after debridement.[342]

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CQ31: IS NEGATIVE-PRESSURE WOUND THERAPY USEFUL FOR THE TREATMENT OF "RED" STAGE PRESSURE ULCERS?

Description of recommendation: NPWT is recommended for stages III and IV pressure ulcers in the "red" stage. Reconsideration is recommended for the indication on infected ulcers.

Recommendation level: 1B.

Commentary:

- There are three RCT[343–345] and one non-randomized study[346] on NPWT for stages III and IV pressure ulcers in "red" stage.[343,345] The evidence levels are II and III, respectively. However, a statistically significant difference could not be demonstrated in any of these studies, comparing NPWT and the controls. The recommendation level is 1B.
- In these reports, control groups were treated with wet-to-dry dressing with Ringer's solution, cadexomer iodine or hydrocolloid dressing. None of the studies revealed a significant difference between NPWT and the controls.
- Meanwhile, there are reports with small numbers of patients, 11 and 10,[347,348] in which NPWT achieved a reduction in size of pressure ulcer (evidence level: IVb, V).
- NPWT is generally not indicated for ulcers with infected foci. Under NPWT, the wound can be washed infrequently and become anaerobic; infection by anaerobic bacteria, such as *P. aeruginosa*, can easily be exacerbated. NPWT has been reported to increase the bacteria count on the wound surface.[349] Osteomyelitis or necrotizing fasciitis may occur.[345,350] During NPWT, the wound should be observed carefully; antibiotics should be administrated without delay. NPWT should be suspended when in doubt of infection.
- V.A.C. Therapy has been marketed in Japan since year 2010, followed by RENASYS Negative-Pressure Wound Therapy, SNAP Therapy System and PICO system for NPWT. These four systems were approved by the Japanese National Health Insurance Program. Until 2010, negative pressure therapy had been performed with handmade instruments prepared by a combination of occlusive dressing materials and aspiration devices. Both commercially available systems and handmade instruments were effective, according to the case reports.
- Health insurance payment can be claimed only on the use of the commercially available devices. The same amount of payment is claimable regardless of products. The claimable period is up to 3 weeks. With written comments on claim, another 1 week of payment can be claimed. For NPWT on outpatients, SNAP Therapy System and PICO system for NPWT can be claimed. The claimable period is the same as that of inpatients. In order to claim the payment, visiting outpatient clinics is mandatory. It is not available for patients only receiving home care.

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ARE THE PRESSURE ULCERS IMPROVED? CQ32: HOW SHOULD PRESSURE ULCERS BE ASSESSED?

Description of recommendation: The use of the DESIGN® (1C), DESIGN-R (1C), the Pressure Ulcer Scale for Healing (PUSH)

(1C) or the Pressure Sore Status Tool (PSST) (1C) is recommended for the assessment of pressure ulcers.

Recommendation level: DESIGN, DESIGN-R, PUSH, PSST (1C).

Commentary:

- There is one case–control study concerning the PSST as a method for the assessment of pressure ulcers,[351] and so the evidence level is IVb. Concerning the PUSH, there are three prospective cohort studies,[352–354] and so the evidence level is IVa. For the DESIGN, there is one case–control study,[355] and so the evidence level is IVb. There are three cohort studies regarding the revision of DESIGN, DESIGN-R,[356–358] and so the evidence level is IVa. The recommendation level was set at 1C, because the assessment of the wound is essential for its management.
- The PSST,[351] PUSH,[352] Pressure Ulcer Healing Process (PUHP),[359] DESIGN[360] and its revision, DESIGN-R[361] are known as methods for evaluating pressure ulcers.
- The interrater reliability of the PSST has been reported to be high at 0.91,[351] but it is difficult to use in clinical situations due to the large number of items to be evaluated. The PUSH was devised to overcome this shortcoming. The PUSH score decreased significantly in healing pressure ulcers but did not in those that did not heal. The PUSH score was also closely correlated with the area of pressure ulcer and the PSST score.[352–354] Also, principal component analysis showed that 58–74% of the changes observed in wound healing during a 10-week period could be explained by PUSH items.[362] Another report investigating the use of the PUSH rated the system to be practically usable and reliable in clinical settings.[363]
- The DESIGN is an assessment tool for pressure ulcers developed and publicized by the Japanese Society of Pressure Ulcers in 2002. Its interrater reliability was very high at 0.98 according to judgments using photographs and 0.91 in actual patients, and its score strongly correlated with the PSST score.[355] Although the DESIGN was useful for following up the course of treatment for a particular pressure ulcer, it could not be used for comparison between multiple pressure ulcers. Therefore, it was supplemented in 2008 with the DESIGN-R,[356,361] in which each item of the DESIGN is weighted[364] to compare the severity of multiple possible pressure ulcers according to the score. Subsequently, it was shown that an improvement in the total score in DESIGN-R correlated with healing of the pressure ulcer and that changes in the total score were useful in evaluating the prognosis of the pressure ulcer.[357] Furthermore, the total score has been reported to be able to predict healing time.[358]

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OTHER TREATMENT OPTIONS
CQ33: WHEN SHOULD SURGICAL TREATMENTS FOR WOUND CLOSURE BE PERFORMED?

Description of recommendation: Surgical treatment is recommended for pressure ulcers at stage III and above, but it should be performed after careful evaluation of the patient's general condition and indications. In addition, measures for infection control and surgical and/or chemical debridement should be performed in advance.

Recommendation level: 1C.

Commentary:

- There are retrospective cohort studies[365–370]and a case report[371]in the published work concerning surgical treatments. The evidence level is IVa and the recommendation level is 1C.
- Surgical procedures by skin grafting or flap surgery are effective for inducing early cure of pressure ulcers that are not expected to be cured by non-surgical treatments or require long-term treatment. Careful evaluation of

indications is necessary because they are invasive procedures, particularly musculocutaneous and fasciocutaneous flap surgery.[365] Also, preoperative checking of the patient's general condition, results of blood tests (cell counts, clotting factors) and the presence of medications including antiplatelet agents and anticoagulants are important. According to the guidelines regarding cardiovascular diseases, the continuation of such medications is recommended for minor operations, in which bleeding can be readily controlled.[372] Guidelines for cerebral infarction also mention that "oral administration of" warfarin "is desirable" and that antiplatelet therapy "may be continued".[373] However, as these medications can be suspended in some patients, it is desirable to first consult with the attending physician and to manage patients individually.

- Pressure ulcers do not occur without a cause. Patient conditions such as restriction of locomotion, nutritional state and cardiopulmonary function often persist after surgery. In addition, even if attentive care is possible during hospitalization including frequent body repositioning and the use of body pressure-dispersion devices, the quality of management often reverts to its original level after discharge. Recurrence is likely without sufficient assessment with the patient of his/her environment at home after discharge, and there are cases where the improvement in the patient's condition barely outlasts the hospital stay, an outcome that could only serve the self-satisfaction of the hospital staff. Possibly reflecting such a situation, the postoperative recurrence rate even exceeded 70% in some reports.[366–369]
- Appropriate references should be consulted for the specific techniques used during surgery. The principle is to perform wound bed preparation by surgical debridement or chemical debridement using an enzyme preparation (a few weeks before reconstructive surgery, if possible) and then to select from among split-thickness skin grafting, full-thickness skin grafting, fasciocutaneous flap surgery (perforator flap), musculocutaneous flap surgery and similar procedures considering the outlook for bearing weight and scar contracture. There is a report that the results of fasciocutaneous flap surgery were superior to those of musculocutaneous flap surgery.[370]Some patients may require urinary tract diversion or ostomy.[371]

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CQ34: CAN "WRAP THERAPY" BE USED FOR PRESSURE ULCERS?

Description of recommendation: Wrap therapy is proposed as an option after having carefully considered the indications. However, as the user is liable for the use of a material not approved for medical use such as kitchen cling film wrap, consent must be obtained from the patient and family before treatment.

Recommendation level: 2B.

Commentary:

- There is one RCT reporting on the use of wrap therapy and ordinary treatment.[374] In a multicenter, prospective RCT, 66 patients at 15 hospitals with stage II and stage III ulcers were divided into a group of 31 who received conventional treatment and a group of 35 who underwent wrap therapy. After treatment, a comparison of healing time and rate of change of the pressure ulcer scale showed no significant difference, and so the recommendation level is 2B.
- In addition, there are two non-randomized comparison studies reporting that wrap therapy significantly contributes to improvements in the wound condition,[375,376] and the evidence level is III.
- However, there is a case series study collecting cases of adverse events caused by wrap therapy for stage IV pressure ulcers,[377] and so the indications for this treatment must be considered with great care.
- Occlusive dressing is a dressing method used to avoid drying of the wound in the expectation of moist wound healing. It is a general term for dressing methods using modern wound-dressing materials rather than conventional gauze dressing. It specifically refers to using materials that occlude the wound surface and create a moist environment such as hydrocolloids; materials that moisten dried wounds such as hydrogels; and materials that absorb and retain exudates such as alginate, chitin, Hydrofiber, hydropolymer, polyurethane foam or secondary dressing materials such as polyurethane film.[378]
- Wound-dressing methods that prevent the entry of liquids, oxygen and bacteria into the wound from outside, and leakage or evaporation of exudate from the wound, are types of occlusive dressing methods, but they may be more

accurately referred to as closed or sealed dressing methods. By contrast, dressing methods that allow the passage of vapor and oxygen are semi-occlusive or semipermeable, but because the boundary between the two is not distinct, these are all commonly referred to as occlusive dressing methods without making such a distinction.[378]

- Wrap therapy, a dressing method using polychlorovinylidene kitchen cling film wrap with low permeability to oxygen and water vapor, can be an occlusive dressing unlike semi-occlusive dressings using a polyurethane film, but because the material itself is not adhesive it does not seal the wound.[375,376,378] Advocates of wrap therapy call the method an "open wet dressing", as excess exudates escape from the wound due to the incomplete seal.[378,379]
- There are various dressing methods under the umbrella of wrap therapy or open wet dressing, and no established protocols exist. Therefore, it is difficult to judge whether or not wrap therapy as a whole has value. However, a non-randomized comparison study showed that dressing using polychlorovinylidene significantly improved pressure ulcers compared with conventional treatment and that no significant difference was noted in the occurrence of infection.[375] As a result, it is conceivable that the method is effective when the protocol used in this study is applied.
- Because kitchen cling film wrap is not approved as a medical material, physicians must be aware that they are responsible for any resulting damage to health, and that consent must be obtained from the patient and family.

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CQ35: WHAT LOCAL TREATMENTS ARE PERFORMED OTHER THAN SURGICAL TREATMENT AND WRAP THERAPY?

Description of recommendation: Hydrotherapy (1A), infrared-visual light therapy (1A), low-power laser therapy (1B) and hyperbaric oxygen therapy (1C) are recommended. In addition, ultraviolet therapy (2A) and electric stimulation therapy (2A) are proposed as options.

Recommendation levels: 1A, 1B, 1C, 2A.

Hydrotherapy, infrared-visual light therapy (1A).

Low-power laser therapy (1B).

Hyperbaric oxygen therapy (1C).

Ultraviolet therapy, electric stimulation therapy (2A).

Commentary:

- There is one RCT evaluating hydrotherapy.[380] The evidence level is II and the recommendation level is 1A. There is one RCT on infrared therapy.[381] The evidence level is II and the recommendation level is 1A. There is one RCT on low-power laser therapy.[382] The evidence level is II, but there was no difference compared with the control group so the recommendation level is 1B. There is one case study on hyperbaric oxygen therapy.[383] The evidence level is V and the recommendation level is 1C. There is one RCT on ultraviolet therapy.[384] The evidence level is II, but a Kromayer lamp was used that is no longer available, and so the recommendation level was set at 2A. There is a meta-analysis[385] and RCT on electric stimulation therapy. The evidence level is I, but its use for pressure ulcers is not covered by the National Health Insurance in Japan so the recommendation level was set to 2A.
- There is an RCT on hydrotherapy[380] resulting in a significant decrease in wound area compared with saline gauze dressing as a control, and the mechanism of its effect is not discussed. In this therapy, the physical stimulation of a water vortex or water warmed to an insensible temperature (35.5–36.6°C) is applied to the entire body (Hubbard tank method) or part of the body (vortex bathing method).
- Of the types of phototherapy, infrared therapy has the most reports evaluating the effects on wound healing. The RCT performed for pressure ulcers showed a significantly faster cure compared with the control group.[381] However, the wavelength band of infrared rays emitted differs depending on the apparatus used, and so there is no conclusion about which bands are effective. It was reported in an RCT that low-power laser therapy did not produce a difference in pressure ulcer treatment compared with the non-exposed group.[382] In a blinded RCT on ultraviolet therapy, a Kromayer lamp was used. The exposure dose started at 2.5 minimal erythema dose twice per week, and gradually increased to maintain an erythema, which was shown to promote wound healing in the treated group. The number of subjects in each group was only eight, which is low.[384] Looking at the Cochrane Database Systematic Review for phototherapies as a whole, the beam sources, evaluation methods, risk evaluation and similar procedures are widely divergent depending on the study, and so an overall evaluation cannot be made.[388]
- Hyperbaric oxygen therapy is performed by placing the patient in a chamber with an elevated oxygen pressure for the treatment of carbon monoxide poisoning or anaerobic bacterial infection. There are case reports of its use for

treating pressure ulcers,[383,394] but there is no evidence that it is more useful than conventional treatments.

- Electric stimulation therapy for pressure ulcers is not covered by the National Health Insurance in Japan, and so it is rarely used, but a meta-analysis reports its efficacy.[385] However, there is also a placebo-controlled multicenter collaborative double-blind RCT (63 cases) reporting that the wound area decreased more rapidly up to the 45th day of follow up, but that there was no significant difference in the wound area decrease rate, cure rate or period until cure at the endpoint (147th day).[386] This therapy aims to promote wound healing by passing an electric current between the wound and electrodes attached around the wound. Because sodium ions gather at the negative electrode, the pH of the area near this electrode becomes alkaline, and the area near the positive electrode becomes acidic. These changes in the pH near the electrodes are believed to affect bacterial infection and vasodilation at the wound. Also, when electricity is applied, negatively charged cells such as macrophages and neutrophils migrate toward the positive electrode, and positively charged cells such as fibroblasts migrate toward the negative electrode. This phenomenon of particular cells being attracted to electrodes is known as electrotaxis.
- There is one meta-analysis showing a significant improvement in pressure ulcers in spinal cord injury patients by electric stimulation of the gluteus maximus muscle.[385] In addition to the above, its mechanism is indicated in a number of reports to result from reduced sitting pressure as a result of the electrical stimulus.[389–392] An increase in localized cutaneous blood flow after electric stimulation has been reported along with an associated significant decrease in sitting pressure in patients with spinal cord injury.[393]
- Other than the above therapies, treatment for chronic wounds such as the administration of an angiogenic or cell growth factor or the administration of autologous cells for those same purposes has recently being developed. As for drugs, vascular endothelial growth factor,[395] platelet-derived growth factor (PDGF)[396] and GM-CSF[397] are being used in addition to basal fibroblast growth factor (bFGF; see CQ29), which has already been approved for clinical use. These agents are administrated locally or as a plasmid by i.m. injection. There have been studies of localized administration of PDGF to pressure ulcers, and a small number of RCT have found a significant reduction in treatment time.[397] In addition, clinical trials of a treatment for stasis ulcers using virus vectors are in progress in the USA.
- Because blood and blood cells include cell growth factors, a solution prepared from platelets[398] or stored heparinized blood[399] is applied locally with a sealed dressing to treat wounds. In addition, because the vascular endothelium is derived from bone marrow cells, autologous hematopoietic stem cells are administrated primarily in conditions involving ischemia in the limbs with the main objective of stimulating angiogenesis.[400] No clinical study has been conducted concerning the administration of stem cells for pressure ulcers, and so it is considered a treatment for the future.
- It has been reported that skin ulcer healing was promoted by applying a cultured dermal substitute formed by culturing human fibroblasts in a collagen sponge. A resulting healing effect on pressure ulcers has been reported in five patients.[401] In addition, applying the result of filling a gel base with bone marrow cells[402] and bFGF[403] is also being attempted.

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